This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

KOKAI (Japanese Unexamined Patent Publication) No. 11-80156
Title of the Invention: 1-(Substituted Aryl)Alkyl-1H-Imidazopyridine-4-Amine Derivatives
Publication Date: March 26, 1999
Patent Application No. 9-255926
Filing Date: September 4, 1997
Applicant: Hokuriku Seiyaku Co., Ltd.

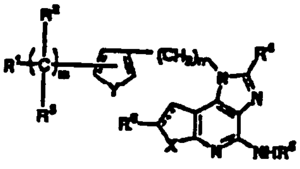
[ABSTRACT]

[OBJECT]

To provide compounds with excellent interferon inductivity.

[SOLUTION MEANS]

A 1-(substituted aryl)alkyl-1H-imidazo[4,5-c]quinoline-4-amine derivative represented by general formula (I):

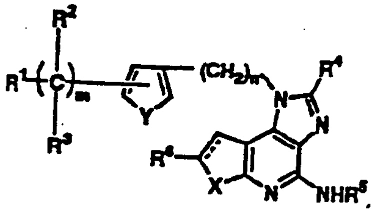


(I)

wherein R^1 is a group COR^7, SO$_2$NR^{8}R^9, NR^{10}R^{11}, etc., R^2 and R^3 are hydrogen atoms or alkyl groups; R^4 is a hydrogen atom, alkyl group, etc.; R^5 is a hydrogen atom or alkyl group; R^6 is a hydrogen atom, alkyl group, etc.; R^7 is a hydroxyl group, alkyl group or alkoxy group; R^8 and R^9 are hydrogen atoms or alkyl groups; R^{10} is a hydrogen atom, alkyl group, etc.; R^{11} is a hydrogen atom, alkyl group, alkanesulfonyl group, etc.; m is 0-1, n is an integer of 1-3; X is an alkylene chain or the carbon chain represented by CH=CH; Y is a sulfur atom or the carbon chain represented by CH=CH; and the bonds shown by solid lines and dotted lines represent single bonds or double bonds, or a pharmacologically acceptable salt thereof.

CLAIMS

1. A 1-(substituted aryl)alkyl-1H-imidazopyridine-4-amine derivative represented by the following general formula (I):



(I)

wherein R^1 is a group represented by COR^7, $SO_2NR^8R^9$, $CONR^8R^9$, $NR^{10}R^{11}$ or $C(R^{12})=NOH$, or a hydroxyl group or cyano group; R^2 and R^3 are the same or different and represent hydrogen atoms or lower alkyl groups; R^4 represents a hydrogen atom or a linear or branched alkyl group of 1-10 carbon atoms which may be substituted with one or more hydroxyl groups, lower alkoxy groups, cyclic alkyl groups or halogen atoms; R^5 represents a hydrogen atom or lower alkyl group; R^6 represents a hydrogen atom, lower alkyl group, lower alkoxy group or halogen atom; R^7 represents a hydroxyl group, lower alkyl group or lower alkoxy group; R^8 and R^9 are the same or different and represent hydrogen atoms or lower alkyl groups; R^{10} represents a hydrogen atom, lower alkyl group or benzyl group; R^{11} represents a hydrogen atom, lower alkyl group, benzyl group, lower alkanesulfonyl group, lower alkanoyl group, substituted or unsubstituted carbamoyl group, substituted or unsubstituted thiocarbamoyl group or substituted or unsubstituted benzenesulfonyl group; R^{12} represents a hydrogen atom or lower alkyl group; m represents an integer of 0-1, n represents an integer of 1-3; X represents an alkylene chain of 1-3 carbon atoms or the carbon chain represented by CH=CH; Y represents a sulfur atom or the carbon chain represented by CH=CH; and the bonds shown by solid lines and dotted lines are single bonds or double bonds, or a pharmacologically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Technical Field of the Invention

The present invention relates to a novel 1-(substituted aryl)alkyl-1H-imidazopyridine-4-amine derivative or pharmacologically acceptable salt thereof, which induces biosynthesis of interferon and is useful as an antiviral agent or anticancer drug.

Prior Art

Compounds with a 1H-imidazopyridine-4-amine skeleton have been disclosed, such as the compounds with anti-viral action mentioned in Japanese Unexamined Patent Publication No. 60-123488, including 1-isobutyl-1H-imidazo[4,5-c]quinoline-4-amine (common name: imiquimod) and 1-(2-phenylethyl)-1H-imidazo[4,5-c]quinoline-4-amine, but absolutely no 1H-imidazopyridine-4-amine derivatives have hitherto been known having substituents with functional groups such as sulfamoyl, carbamoyl, amino, amido, sulfonamide, cyano, carboxyl, ureido, thioureido, hydroxyiminomethyl or hydroxyl groups on the aromatic ring of the primary arylalkyl group, such as according to the present invention.

Problems to be Solved by the Invention

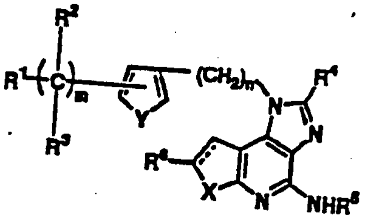
The aforementioned imiquimod is known to have interferon biosynthesis-inducing action as described in Journal of Interferon Research, Vol.14, p.81 (1994) and elsewhere, while compounds with similar action are also known, such as 2-amino-5-bromo-6-phenyl-4(3H)-pyrimidinone (common name: bropirimine) [Journal of Medicinal Chemistry, Vol.23, p.237 (1980)] and 2,7-bis[2-(diethylamino)ethoxy]-9H-fluoren-9-one (common name: tilorone) (The Merck Index, 12th Edition, 9581); however, as of the time of this writing it cannot be said that their activities are sufficient.

It is an object of the present invention to provide novel compounds with excellent interferon inductivity which are useful for diseases caused by viruses, such as rheumatoid arthritis, warts, hepatitis B, hepatitis C, etc. and for cancer and other neoplastic diseases.

Means for Solving the Problems

As a result of diligent research aimed at achieving the object described above, the present inventors have completed the present invention upon the finding that novel 1-(substituted aryl)alkyl-1H-imidazopyridine-4-amine derivatives having substituents with functional groups such as sulfamoyl, carbamoyl, amino, amido, sulfonamide, cyano, carboxyl, ureido, thioureido, hydroxyiminomethyl or hydroxyl groups on the aromatic ring of the primary arylalkyl group, and pharmacologically acceptable salts thereof, have excellent interferon inductivity.

In other words, the present invention relates to 1-(substituted aryl)alkyl-1H-imidazopyridine-4-amine derivatives represented by the following general formula (I):



(I)

wherein R^1 is a group represented by COR^7, $SO_2NR^8R^9$, $CONR^8R^9$, $NR^{10}R^{11}$ or $C(R^{12})=NOH$, or a hydroxyl group or cyano group; R^2 and R^3 are the same or different and represent hydrogen atoms or lower alkyl groups; R^4 represents a hydrogen atom or a linear or branched alkyl group of 1-10 carbon atoms which may be substituted with one or more hydroxyl groups, lower alkoxy groups, cyclic alkyl groups or halogen atoms; R^5 represents a hydrogen atom or lower alkyl group; R^6 represents a hydrogen atom, lower alkyl group, lower alkoxy group or halogen atom; R^7 represents a hydroxyl group, lower alkyl group or lower alkoxy group; R^8 and R^9 are the same or different and represent hydrogen atoms or lower alkyl groups; R^{10} represents a hydrogen atom, lower alkyl group or benzyl group; R^{11} represents a hydrogen atom, lower alkyl group, benzyl group, lower alkanesulfonyl group, lower alkanoyl group, substituted or unsubstituted carbamoyl group, substituted or unsubstituted thiocarbamoyl group or substituted or unsubstituted benzenesulfonyl group; R^{12} represents a hydrogen atom or lower alkyl group; m represents an integer of 0-1, n represents an integer of 1-3; X represents an alkylene chain of 1-3 carbon atoms or the carbon chain represented by CH=CH; Y represents a sulfur atom or the carbon chain represented by CH=CH; and the bonds shown by solid lines and dotted lines are single bonds or double bonds, and pharmacologically acceptable salts thereof.

[Preferred Mode of the Invention]

As examples of lower alkyl groups represented by R^2, R^3, R^5, R^6, R^7, R^8, H^9, R^{10}, R^{11} or R^{12} in general formula (I) above there may be mentioned methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, etc., as examples of linear or branched alkyl groups of 1-10 carbon atoms represented by R^4 there may be mentioned methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, etc., as examples of lower alkoxy groups which may be substituted on these alkyl groups there may be mentioned methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc., as examples of cyclic alkyl groups which may be substituted on these alkyl groups there may be mentioned cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc., and as examples of halogen atoms which may be substituted on these alkyl groups there may be mentioned fluorine, chlorine, bromine and iodine. As examples of lower alkoxy groups represented by R^6 and R^7 there may be mentioned methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc., and as examples of halogen atoms represented by R^6 there may be mentioned fluorine, chlorine, bromine and iodine. As lower alkanesulfonyl groups represented by R^{11} there may be mentioned methanesulfonyl, propanesulfonyl, butanesulfonyl, etc., and as lower alkanoyl groups represented by R^{11} there may be mentioned acetyl, propionyl, butyryl, etc. As examples of substituents on the substituted or unsubstituted carbamoyl group, substituted or unsubstituted thiocarbamoyl group or substituted or unsubstituted benzenesulfonyl group represented by R^{11} there may be mentioned lower alkyl groups, lower alkoxy groups, halogen atoms, etc.

The compounds represented by general formula (I) above according to the invention may be converted to pharmacologically acceptable salts, and the bases may also be dissociated from the produced salts, depending on the need.

As examples of pharmacologically acceptable salts of the compounds represented by general formula (I) above according to the invention there may be mentioned acid addition salts, as well as mineral acid salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid, etc. and organic acid salts of acetic acid, maleic acid, fumaric acid, citric acid, oxalic acid, malic acid, methanesulfonic acid, p-toluenesulfonic acid, mandelic acid, 10-camphor sulfonic acid, tartaric acid, etc.

Optical isomers may be present for compounds with asymmetric carbons among the compounds represented by general formula (I) above according to the invention, and these optically active species and their mixtures are also encompassed by the present invention.

Also, the compounds represented by general formula (I) above according to the invention and their pharmacologically acceptable salts may exist in any desired crystalline form depending on the production conditions or they may exist as any desired hydrates, and these crystalline forms and hydrates, as well as mixtures thereof, are also encompassed by the present invention.

As preferred modes of the 1-(substituted aryl)alkyl-1H-imidazopyridine-4-amine derivatives of the invention there may be mentioned the compounds mentioned in the examples provided below, as well as the following compounds and their pharmacologically acceptable salts, with the understanding that the invention is not limited to these.

(1) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(2) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-methyl-1H-imidazo[4,5-c]quinoline-4-amine

(3) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethyl-1H-imidazo[4,5-c]quinoline-4-amine

(4) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(5) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-n-butyl-1H-imidazo[4,5-c]quinoline-4-amine

(6) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-cyclopropylmethyl-1H-imidazo[4,5-c]quinoline-4-amine

(7) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethoxymethyl-1H-

imidazo[4,5-c]quinoline-4-amine

(8) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(9) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-1H-imidazo[4,5-c]quinoline-4-amine

(10) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(11) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-6,7,8,9-tetrahydro-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(12) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-n-butyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(13) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-cyclopropylmethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(14) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethoxymethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(15) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(16) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1,6,7,8-tetrahydro-2-methylcyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(17) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(18) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1,6,7,8-tetrahydro-2-n-propylcyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(19) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-n-butyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(20) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-cyclopropylmethyl-1,6,7,8-tetrahydrocyclopenta [b]imidazo[4,5-d]pyridine-4-amine

(21) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethoxymethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(22) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(23) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1,6,7,8,9,10-hexahydro-2-methylcyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(24) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(25) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1,6,7,8,9,10-hexahydro-2-n-propylcyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(26) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-n-butyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(27) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-cyclopropylmethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(28) 1-[2-[4-(1-aminoethyl)phenyl]ethyl]-2-ethoxymethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(29) N-[1-[4-[2-(4-amino-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(30) N-[1-[4-[2-(4-amino-2-methyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(31) N-[1-[4-[2-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(32) N-[1-[4-[2-(4-amino-2-n-propyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(33) N-[1-[4-[2-(4-amino-2-n-butyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(34) N-[1-[4-[2-(4-amino-2-cyclopropylmethyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(35) N-[1-[4-[2-(4-amino-2-ethoxymethyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(36) N-[1-[4-[2-(4-amino-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(37) N-[1-[4-[2-(4-amino-6,7,8,9-tetrahydro-2-methyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(38) N-[1-[4-[2-(4-amino-2-ethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(39) N-[1-[4-[2-(4-amino-6,7,8,9-tetrahydro-2-n-propyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(40) N-[1-[4-[2-(4-amino-2-n-butyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide

(41) N-[1-[4-[2-(4-amino-2-cyclopropylmethyl-6,7,8,9-tetrahydro-

1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide
(42) N-[1-[4-[2-(4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl]ethyl] acetamide
(43) N-[1-[4-[2-(4-amino-1,6,7,8-tetrahydrocyclopenta[b] imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl]ethyl] acetamide
(44) N-[1-[4-[2-(4-amino-1,6,7,8-tetrahydro-2-methylcyclopenta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(45) N-[1-[4-[2-(4-amino-2-ethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(46) N-[1-[4-[2-(4-amino-1,6,7,8-tetrahydro-2-n-propylcyclopenta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(47) N-[1-[4-[2-(4-amino-2-n-butyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(48) N-[1-[4-[2-(4-amino-2-cyclopropylmethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(49) N-[1-[4-[2-(4-amino-2-ethoxymethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(50) N-[1-[4-[2-(4-amino-1,6,7,8,9,10-hexahydrocyclohepta [b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl]ethyl] acetamide
(51) N-[1-[4-[2-(4-amino-1,6,7,8,9,10-hexahydro-2-methylcyclohepta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(52) N-[1-[4-[2-(4-amino-2-ethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(53) N-[1-[4-[2-(4-amino-1,6,7,8,9,10-hexahydro-2-n-propylcyclohepta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide
(54) N-[1-[4-[2-(4-amino-2-n-butyl-1,6,7,8,9,10-

hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide

(55) N-[1-[4-[2-(4-amino-2-cyclopropylmethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl]ethyl] acetamide

(56) N-[1-[4-[2-(4-amino-2-ethoxymethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl]ethyl] acetamide

(57) 1-[2-[4-(aminomethyl)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(58) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-methyl-1H-imidazo[4,5-c]quinoline-4-amine

(59) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethyl-1H-imidazo[4,5-c]quinoline-4-amine

(60) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(61) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-n-butyl-1H-imidazo[4,5-c]quinoline-4-amine

(62) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-cyclopropylmethyl-1H-imidazo[4,5-c]quinoline-4-amine

(63) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethoxymethyl-1H-imidazo[4,5-c]quinoline-4-amine

(64) 1-[2-[4-(aminomethyl)phenyl]ethyl]-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(65) 1-[2-[4-(aminomethyl)phenyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-1H-imidazo[4,5-c]quinoline-4-amine

(66) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(67) 1-[2-[4-(aminomethyl)phenyl]ethyl]-6,7,8,9-tetrahydro-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(68) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-n-butyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(69) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-cyclopropylmethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(70) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethoxymethyl-6,7,8,9-

tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(71) 1-[2-[4-(aminomethyl)phenyl]ethyl]-1,6,7,8-tetrahydrocycl penta[b]imidazo[4,5-d]pyridine-4-amine

(72) 1-[2-[4-(aminomethyl)phenyl]ethyl]-1,6,7,8-tetrahydro-2-methylcyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(73) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(74) 1-[2-[4-(aminomethyl)phenyl]ethyl]-1,6,7,8-tetrahydro-2-n-propylcyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(75) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-n-butyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(76) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-cyclopropylmethyl-1,6,7,8-tetrahydrocyclopenta [b]imidazo[4,5-d]pyridine-4-amine

(77) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethoxymethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(78) 1-[2-[4-(aminomethyl)phenyl]ethyl]-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(79) 1-[2-[4-(aminomethyl)phenyl]ethyl]-1,6,7,8,9,10-hexahydro-2-methylcyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(80) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethyl-1,6,7,8,9,10-hexahydrocyclohepta-[b]imidazo[4,5-d]pyridine-4-amine

(81) 1-[2-[4-(aminomethyl)phenyl]ethyl]-1,6,7,8,9,10-hexahydro-2-n-propylcyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(82) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-n-butyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(83) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-cyclopropylmethyl-1,6,7,8,9,10-hexahydrocyclohepta[b] imidazo[4,5-d]pyridine-4-amine

(84) 1-[2-[4-(aminomethyl)phenyl]ethyl]-2-ethoxymethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(85) 1-[2-(4-aminophenyl)ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(86) 1-[2-(4-aminophenyl)ethyl]-2-methyl-1H-imidazo[4,5-c]quinoline-4-amine

(87) 1-[2-(4-aminophenyl)ethyl]-2-ethyl-1H-imidazo[4,5-c]quinoline-4-amine

(88) 1-[2-(4-aminophenyl)ethyl]-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(89) 1-[2-(4-aminophenyl)ethyl]-2-n-butyl-1H-imidazo[4,5-c]quinoline-4-amine

(90) 1-[2-(4-aminophenyl)ethyl]-2-cyclopropylmethyl-1H-imidazo[4,5-c]quinoline-4-amine

(91) 1-[2-(4-aminophenyl)ethyl]-2-ethoxymethyl-1H-imidazo[4,5-c]quinoline-4-amine

(92) 1-[2-(4-aminophenyl)ethyl]-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(93) 1-[2-(4-aminophenyl)ethyl]-6,7,8,9-tetrahydro-2-methyl-1H-imidazo[4,5-c]quinoline-4-amine

(94) 1-[2-(4-aminophenyl)ethyl]-2-ethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(95) 1-[2-(4-aminophenyl)ethyl]-6,7,8,9-tetrahydro-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(96) 1-[2-(4-aminophenyl)ethyl]-2-n-butyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(97) 1-[2-(4-aminophenyl)ethyl]-2-cyclopropylmethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(98) 1-[2-(4-aminophenyl)ethyl]-2-ethoxymethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-4-amine

(99) 1-[2-(4-aminophenyl)ethyl]-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(100) 1-[2-(4-aminophenyl)ethyl]-1,6,7,8-tetrahydro-2-methylcyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(101) 1-[2-(4-aminophenyl)ethyl]-2-ethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(102) 1-[2-(4-aminophenyl)ethyl]-1,6,7,8-tetrahydro-2-n-propylcyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(103) 1-[2-(4-aminophenyl)ethyl]-2-n-butyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(104) 1-[2-(4-aminophenyl)ethyl]-2-cyclopropylmethyl-1,6,7,8-

tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(105) 1-[2-(4-aminophenyl)ethyl]-2-ethoxymethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(106) 1-[2-(4-aminophenyl)ethyl]-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(107) 1-[2-(4-aminophenyl)ethyl]-1,6,7,8,9,10-hexahydro-2-methylcyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(108) 1-[2-(4-aminophenyl)ethyl]-2-ethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(109) 1-[2-(4-aminophenyl)ethyl]-1,6,7,8,9,10-hexahydro-2-n-propylcyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(110) 1-[2-(4-aminophenyl)ethyl]-2-n-butyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(111) 1-[2-(4-aminophenyl)ethyl]-2-cyclopropylmethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(112) 1-[2-(4-aminophenyl)ethyl]-2-ethoxymethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(113) N-[4-[2-(4-amino-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(114) N-[4-[2-(4-amino-2-methyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(115) N-[4-[2-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(116) N-[4-[2-(4-amino-2-n-propyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(117) N-[4-[2-(4-amino-2-n-butyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(118) N-[4-[2-(4-amino-2-cyclopropylmethyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(119) N-[4-[2-(4-amino-2-ethoxymethyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(120) N-[4-[2-(4-amino-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(121) N-[4-[2-(4-amino-6,7,8,9-tetrahydro-1H imidazo[4,5-

c]quinoline-1-yl)ethyl]phenyl] acetamide

(122) N-[4-[2-(4-amino-2-ethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(123) N-[4-[2-(4-amino-6,7,8,9-tetrahydro-2-n-propyl-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(124) N-[4-[2-(4-amino-2-n-butyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(125) N-[4-[2-(4-amino-2-cyclopropylmethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(126) N-[4-[2-(4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-yl)ethyl]phenyl] acetamide

(127) N-[4-[2-(4-amino-1,6,7,8-tetrahydrocyclopenta [b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(128) N-[4-[2-(4-amino-1,6,7,8-tetrahydro-2-methylcyclopenta [b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(129) N-[4-[2-(4-amino-2-ethyl-1,6,7,8-tetrahydrocyclopenta [b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(130) N-[4-[2-(4-amino-1,6,7,8-tetrahydro-2-n-propylcyclopenta [b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(131) N-[4-[2-(4-amino-2-n-butyl-1,6,7,8-tetrahydro-2-cyclopenta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(132) N-[4-[2-(4-amino-2-cyclopropylmethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridin-1-yl) ethyl]phenyl] acetamide

(133) N-[4-[2-(4-amino-2-ethoxymethyl-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(134) N-[4-[2-(4-amino-1,6,7,8,9,10-hexahydrocyclohepta [b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(135) N-[4-[2-(4-amino-1,6,7,8,9,10-hexahydro-2-methylcyclohepta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(136) N-[4-[2-(4-amino-2-ethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(137) N-[4-[2-(4-amino-1,6,7,8,9,10-hexahydro-2-n-propylcyclohepta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(138) N-[4-[2-(4-amino-2-n-butyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(139) N-[4-[2-(4-amino-2-cyclopropylmethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(140) N-[4-[2-(4-amino-2-ethoxymethyl-1,6,7,8,9,10-hexahydrocyclohepta[b]imidazo[4,5-d]pyridin-1-yl)ethyl]phenyl] acetamide

(141) 1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(142) 2-methyl-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(143) 2-ethyl-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(144) [2-[4-(methylamino)phenyl]ethyl]-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(145) 2-n-butyl-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(146) 2-cyclopropylmethyl-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(147) 2-ethoxymethyl-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(148) 6,7,8,9-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(149) 6,7,8,9-tetrahydro-2-methyl-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(150) 2-ethyl-6,7,8,9-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(151) 6,7,8,9-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]-2-n-propyl-1H-imidazo[4,5-c]quinoline-4-amine

(152) 2-n-butyl-6,7,8,9-tetrahydro-1-[2-[4-(methylamino)

phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(153) 2-cyclopropylmethyl-6,7,8,9-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(154) 2-ethoxymethyl-6,7,8,9-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

(155) 1,6,7,8-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(156) 1,6,7,8-tetrahydro-2-methyl-1-[2-[4-(methylamino)phenyl]ethyl]cyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(157) 2-ethyl-1,6,7,8-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(158) 1,6,7,8-tetrahydro-1-[2-[4-(methylamino)phenyl] ethyl]-2-n-propylcyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(159) 2-n-butyl-1,6,7,8-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(160) 2-cyclopropylmethyl-1,6,7,8-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(161) 2-ethoxymethyl-1,6,7,8-tetrahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclopenta[b]imidazo[4,5-d]pyridine-4-amine

(162) 1,6,7,8,9,10-hexahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(163) 1,6,7,8,9,10-hexahydro-2-methyl-1-[2-[4-(methylamino)phenyl]ethyl]cyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(164) 2-ethyl-1,6,7,8,9,10-hexahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclohepta[b]imidazo[4,5-d]pyridine-4-amine

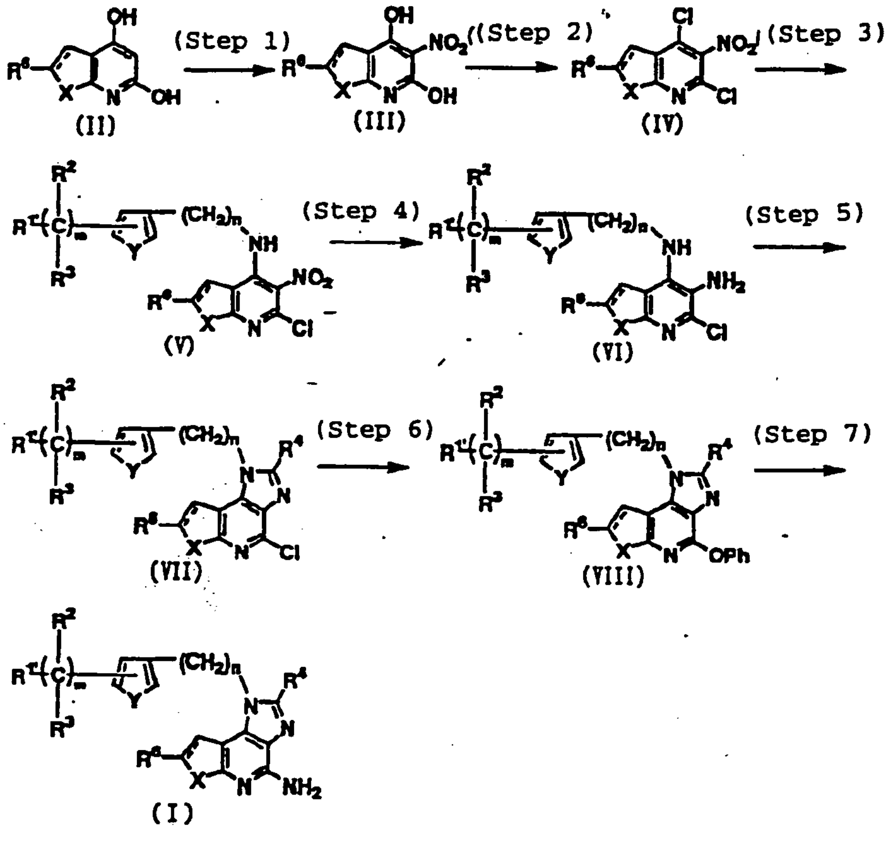
(165) 1,6,7,8,9,10-hexahydro-1-[2-[4-(methylamino)phenyl]ethyl]-2-n-propylcyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(166) 2-n-butyl-1,6,7,8,9,10-hexahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(167) 2-cyclopropylmethyl-1,6,7,8,9,10-hexahydro-1-[2-[4-(methylamino)phenyl]ethyl]cyclohepta[b]imidazo[4,5-d]pyridine-4-amine

(168) 2-ethoxymethyl-1,6,7,8,9,10-hexahydro-1-[2-[4-methylamino)phenyl]ethyl]cyclohepta[b]imidazo[4,5-d]pyridine-4-amine

The novel 1-(substituted aryl)alkyl-1H-imidazopyridine-4-amine derivatives represented by general formula (I) above according to the invention may be produced by any of various different processes. As the first form of a production process for the invention there may be mentioned the following production process which follows the method disclosed in Japanese Unexamined Patent Publication No. 3-206078, which production process allows synthesis of compounds of general formula (I) wherein R^1 is a group represented by $SO_2NR^8R^9$, $CONR^8R^9$ or $NR^{10}R^{11}$ or a hydroxyl group and R^5 is a hydrogen atom, of which R^{10} is a lower alkyl group or benzyl group and R^{11} is a lower alkyl group, benzyl group, lower alkanesulfonyl group, lower alkanoyl group or a substituted or unsubstituted benzenesulfonyl group.



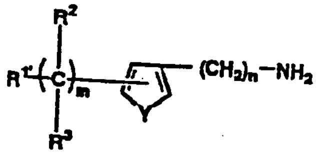
wherein $R^{1'}$ is a group represented by $SO_2NR^8R^9$, $CONR^8R^9$ or $NR^{10'}R^{11'}$ or a hydroxyl group, when $R^{10'}$ is a hydrogen atom $R^{11'}$ is a lower alkanesulfonyl group, lower alkanoyl group, lower alkyl group or a substituted or unsubstituted benzenesulfonyl group, when $R^{10'}$ is a lower alkyl group or benzyl group $R^{11'}$ is a lower alkyl group, benzyl group, lower alkanesulfonyl group, lower alkanoyl group or a substituted or unsubstituted benzenesulfonyl group, and R^2, R^3, R^4, R^6, R^8, R^9, m, n, X, Y and the bonds represented by dotted and solid lines are as defined above.

Compounds represented by general formulas (II) and (III) as starting materials in the production process for the invention are known compounds or commercially available compounds, and their production processes are disclosed in Journal of Medicinal Chemistry, Vol.18, p.726 (1975) and elsewhere.

Specifically, in Step 1 a compound represented by general formula (II) may be reacted in the presence or in the absence of a solvent such as acetic acid, using a nitrating agent such as fuming nitric acid at from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (III).

In Step 2, the compound of general formula (III) may be reacted in the presence or in the absence of an inert solvent such as N,N-dimethylformamide or methylene chloride using a chlorinating agent, for example phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride or phosphorus pentachloride at from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (IV).

In Step 3, an amine represented by the following general formula (IX)



(IX)

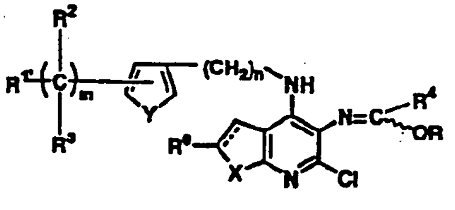
wherein $R^{1'}$, R^2, R^3, m, n and Y are as defined above, production processes for which are disclosed in Japanese Unexamined Patent Publication No. 2-6461, No. 62-116575, No. 59-48447 and No. 52-85137 and Journal of Medicinal Chemistry, Vol.20, p.1212 (1977), etc., may be reacted with a compound of general formula (IV) in an inert solvent such as N,N-dimethylformamide or methylene chloride in the presence or in the absence of a base such as triethylamine or potassium carbonate at from -10°C to the reflux temperature of the solvent, to obtain a compound of general formula (V).

In Step 4, the nitro group of the compound of general formula (V) may be reduced by an appropriate reduction method, for example a catalytic reduction method using a catalyst such as platinum, Raney nickel, palladium carbon, etc., a reduction method using nickel chloride and sodium borohydride or a reduction method using iron powder and hydrochloric acid, to obtain a compound of general formula (VI).

In Step 5, the compound of general formula (VI) may be reacted with a trialkyl orthoester represented by the following general formula (X)

$$R^4C(OR)_3 \qquad (X)$$

wherein R represents a lower alkyl group and R^4 is as defined above, in the presence or in the absence of an acid catalyst such as hydrochloric acid or sulfuric acid and in the presence or in the absence of an inert solvent such as N,N-dimethylformamide or methylene chloride at from 0°C to 200°C, to obtain a compound of general formula (VII) (provided that when $R^{1'}$ of general formula (VI) is a SO_2NH_2 group, $R^{1'}$ represents a group $SO_2N=C(OR)R^4$ due to the reaction conditions). However, depending on the compound, the reaction sometimes proceeds more slowly from the reaction intermediate between general formula (VI) and general formula (VII) which is represented by the following general formula (XI)



(XI)

wherein R, $R^{1'}$, R^2, R^3, R^4, R^6, m, n, X and Y are as defined above, and in such cases the resulting intermediate (XI) may be reacted in the presence or in the absence of an acid catalyst such as p-toluenesulfonic acid and in the presence or in the absence of an inert solvent such as N,N-dimethylformamide, acetonitrile or toluene at from 0°C to 200°C to obtain a compound of general formula (VII).

As an alternative method, the compound of general formula (VI) may be reacted with a compound represented by the following general formula (XII)

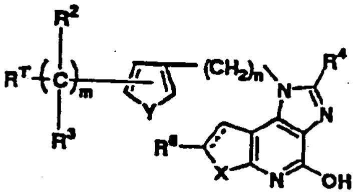
$$R^4COZ \qquad (XII)$$

where Z is a chlorine atom or bromine atom, and R^4 is as defined above, in the presence or in the absence of an acid catalyst such as p-toluenesulfonic acid and in the presence or in the absence of an inert solvent such as N,N-dimethylformamide, acetonitrile or toluene at from 0°C to 200°C to obtain a compound of general formula (VII) (provided that when $R^{1'}$ of general formula (VI) is a hydroxyl group, $R^{1'}$ represents a group $OCOR^4$).

As another alternative method, the compound of general formula (VI) may be reacted with a compound represented by the following general formula (XIII)

$$R^4COOH \qquad (XIII)$$

wherein R^4 is as defined above, in the presence or in the absence of an acid catalyst such as hydrochloric acid or sulfuric acid and in the presence or in the absence of an inert solvent such as N,N-dimethylformamide or methylene chloride at from 0°C to 200°C to obtain a compound of the following general formula (XIV)



(XIV)

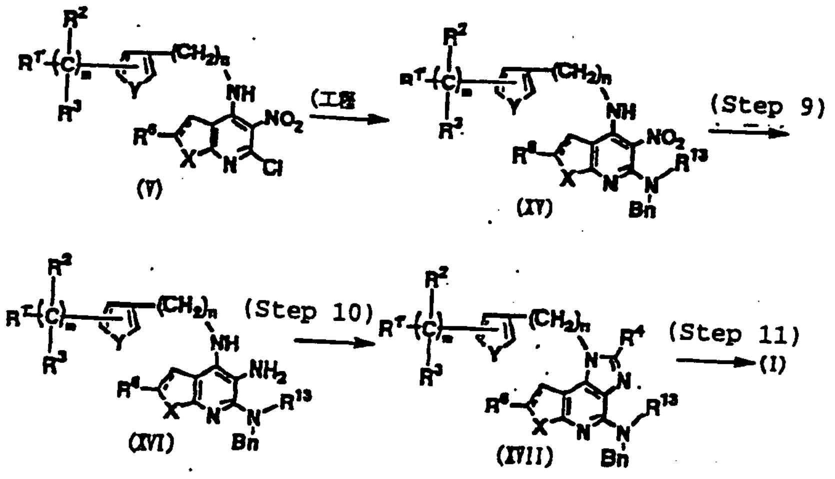
wherein $R^{1'}$ represents a group $OCOR^4$ when $R^{1'}$ of general formula (VI) is a hydroxyl group, and in all other cases $R^{1'}$, R^2, R^3, R^4, R^6, m, n, X and Y are as defined above, after which this compound may be treated with a chlorinating agent to obtain a compound of general formula (VII). For the chlorinating reaction, when R^4 of the compound of general formula (XIV) is a hydrogen atom or a linear or branched alkyl group substituted with a lower alkoxy group, halogen atom or cyclic alkyl group, the compound of general formula (XIV) may be reacted directly with the chlorinating agent, and when R^4 of the compound of general formula (XIV) is a linear or branched alkyl group with one or more hydroxyl groups, it may be reacted with the chlorinating agent after protecting the hydroxyl group(s) with a protecting group such as acetyl (in which case R^4 represents a linear or branched alkyl group having one or more hydroxyl groups protected with a protecting group such as acetyl).

For the chlorinating reaction, a suitable chlorinating agent, for example phosphorus oxychloride, thionyl chloride, phosgene, oxalyl chloride or phosphorus pentachloride, etc. may be reacted therewith in the presence or in the absence of an inert solvent such as N,N-dimethylformamide or methylene chloride at from 0°C to the reflux temperature of the solvent, to obtain a compound of general formula (VII) (provided that when R^4 of general formula (XIV) is a linear or branched alkyl group having one or more hydroxyl groups, R^4 represents a linear or branched alkyl group having one or more hydroxyl groups protected with a protecting group such as acetyl).

In Step 6, the compound of general formula (VII) and phenol may be reacted with an alkali such as sodium hydroxide or potassium hydroxide in the presence or in the absence of an inert solvent such as N,N-dimethylformamide or methylene chloride at from 0°C to 200°C to obtain a compound of general formula (VIII).

In Step 7, the compound of general formula (VIII) may be reacted with ammonium acetate in the presence or in the absence of an inert solvent such as N,N-dimethylformamide or methylene chloride at from 0°C to 200°C to obtain a compound of general formula (I).

As the second form of the production process there may be mentioned the following production process.



wherein R^{13} represents a lower alkyl group or benzyl group, and $R^{1'}$, R^2, R^3, R^4, R^6, m, n, X and Y are as defined above.

Specifically, in Step 8 a compound of general formula (V) obtained by the first form described above and a dibenzylamine or N-lower alkyl-N-benzylamine may be reacted in the presence or in the absence of an inert solvent such as N,N-dimethylformamide or methylene chloride and in the presence or in the absence of a base such as triethylamine or potassium carbonate at from 0°C to 200°C to obtain a compound of general formula (XV).

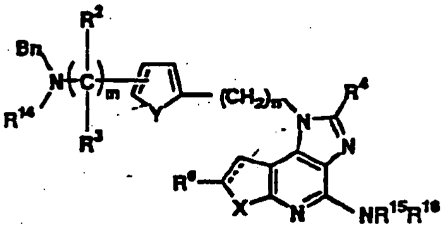
In Step 9, the nitro group of the compound of general formula (XV) may be reduced by an appropriate reduction method, for example a reduction method using nickel chloride and sodium borohydride or a reduction method using iron powder and hydrochloric acid, to obtain a compound of general formula (XVI).

In Step 10, the compound of general formula (XVI) may be reacted with a compound of general formula (X), general formula (XII) or general formula (XIII) in the same manner as step 5 above and under the same conditions, to obtain a compound of general formula (XVII).

In Step 11, the compound of general formula (XVII) may be subjected to debenzylation by an appropriate debenzylating reaction involving, for example, catalytic reduction using a catalyst such as palladium carbon or Perlman's reagent in the presence of a hydrogen donor such as ammonium formate or formic acid, to obtain a compound of general formula (I).

As the third form of the production process there may be mentioned a process of producing a compound of general formula (I) wherein R^1 is a group represented by $NR^{10}R^{11}$ and R^{11} is a hydrogen atom. Specifically, it may be produced by hydrolysis of a compound of general formula (I) that can be obtained by the first form described above wherein R^1 is a group represented by $NR^{10}R^{11}$ and R^{11} is a lower alkanoyl group, in water or an alcoholic solvent such as methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, tert-butanol, etc. or a mixture of water and an alcohol, using an acid such as hydrochloric acid or sulfuric acid or an alkali such as sodium hydroxide or potassium hydroxide in a range from room temperature to the reflux temperature of the solvent.

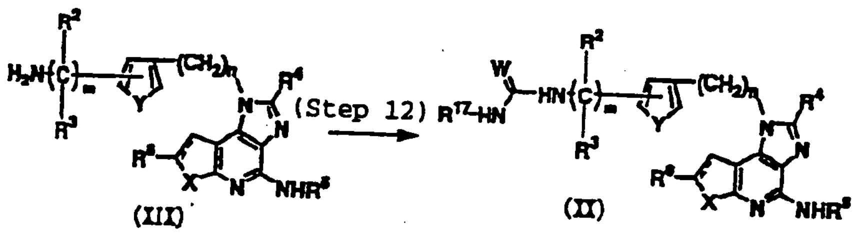
The fourth form of the production process relates to a production process for a compound of general formula (I) wherein R^1 is a group represented by $NR^{10}R^{11}$ and either R^{10} and R^{11} is a hydrogen atom while the other is a hydrogen atom or a lower alkyl group. Specifically, a compound represented by the following general formula (XVIII)



(XVIII)

where R^{14} represents a lower alkyl group or benzyl group, R^{15} represents a hydrogen atom or benzyl group, R^{16} represents a hydrogen atom, lower alkyl group or benzyl group and R^2, R^3, R^4, R^6, m, n, X and Y are as defined above, which can be obtained by the first or second form of the production process described above, may be debenzylated by catalytic reduction or the like using a catalyst such as palladium carbon or Perlman's reagent, in the presence of hydrogen or a hydrogen donor such as formic acid or ammonium formate, to obtain a compound of general formula (I).

As the fifth form of the production process there may be mentioned the following production process.



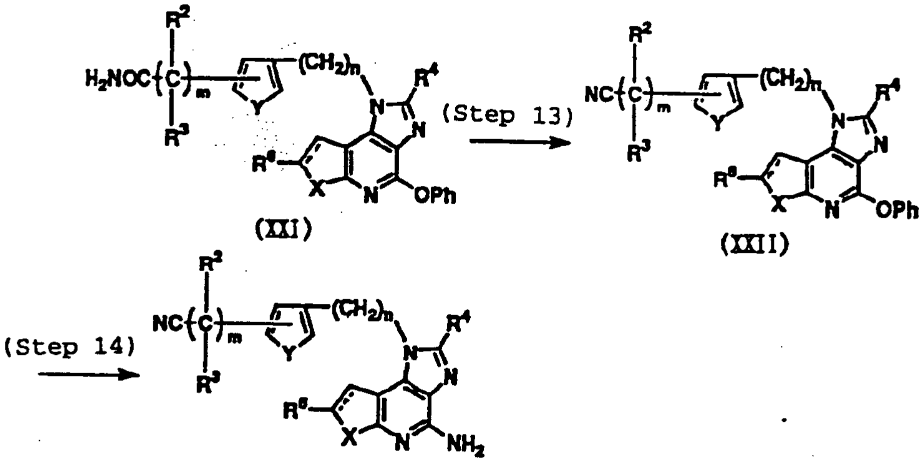
(XIX)

(XX)

wherein R^{17} represents a hydrogen atom or lower alkyl group, W represents an oxygen atom or sulfur atom, and R^2, R^3, R^4, R^5, R^6, m, n, X and Y are as defined above.

Specifically, in Step 12 a compound of general formula (XIX) which can be obtained by the third or fourth form of the production process described above may be reacted with an appropriate ureating agent or thioureating agent in the presence or in the absence of an inert solvent such as N,N-dimethylformamide, acetonitrile or toluene at from 0°C to 200°C, to obtain a compound represented by general formula (XX). As examples of appropriate ureating agents there may be mentioned urea, cyanic acid, sodium cyanate, potassium cyanate, urethane, alkylurethane and alkylisocyanate, and as examples of thioureating agents there may be mentioned thiourethane, alkylthiourethane, alkylisothiocyanate, etc.

As the sixth form of the production process there may be mentioned the following production process.



(XXI)

(XXII)

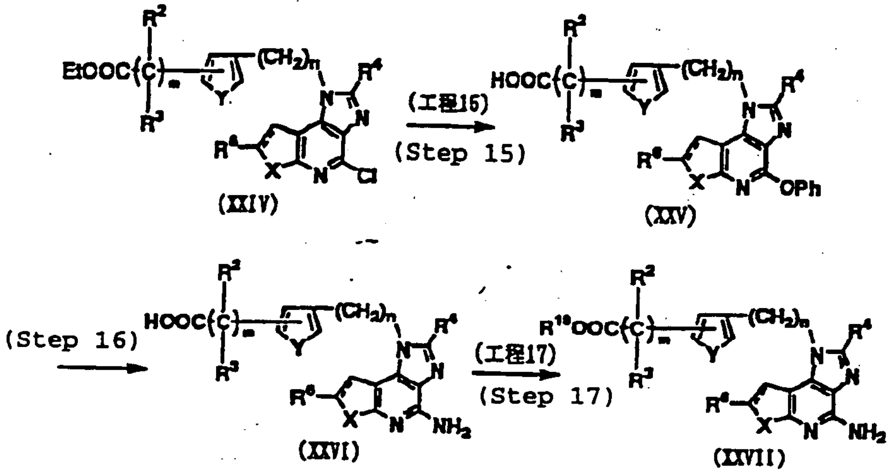
(XXIII)

wherein R^2, R^3, R^4, R^6, m, n, X and Y are as defined above.

Specifically, in Step 13 a compound of general formula (XXI) that can be obtained by the first or second form of the production process described above may be reacted with an appropriate dehydrating agent at from 0°C to 200°C to obtain a compound represented by general formula (XXII). As examples of appropriate dehydrating agents there may be mentioned phosphorus oxychloride, thionyl chloride, diphosphorus pentaoxide, p-toluenesulfonyl chloride, methanesulfonyl chloride, N,N'-dicyclohexylcarbodiimide, acetic anhydride, trifluoroacetic anhydride, etc.

In Step 14, the compound of general formula (XXII) may be reacted by the same method as in Step 7 above to obtain a compound represented by general formula (XXIII).

As the seventh form of the production process there may be mentioned the following production process.

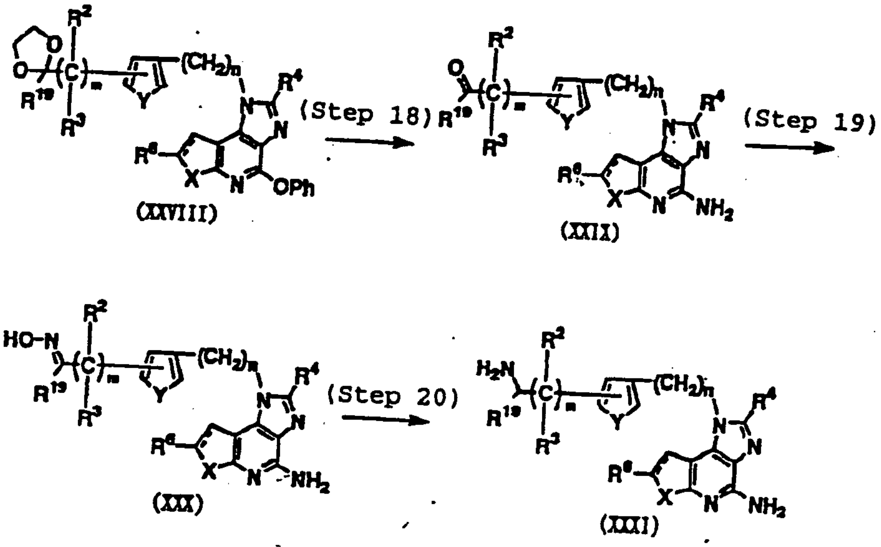


wherein R^{10} represents a lower alkyl group, and R^2, R^3, R^4, R^6, m, n, X and Y are as defined above.

Specifically, in Step 15 a compound of general formula (XXIV) that can be obtained by the first form of the production process described above may be reacted by the same method as in Step 6 above to obtain a compound represented by general formula (XXV), and in Step 16 the compound of general formula (XXV) may be reacted by the same method as in Step 7 above to obtain a compound represented by general formula (XXVI).

In step 17, the compound of general formula (XXVI) may be reacted with an alcohol such as methanol or ethanol in the presence of an appropriate acid catalyst in a range from room temperature to the reflux temperature of the solvent, to obtain a compound represented by general formula (XXVII). As examples of appropriate acid catalysts there may be mentioned concentrated hydrochloric acid, concentrated sulfuric acid, thionyl chloride and alcoholic hydrogen chloride.

As the eighth form of the production process there may be mentioned the following production process.



wherein R^{19} represents a lower alkyl group, and R^2, R^3, R^4, R^6, m, n, X and Y are as defined above.

Specifically, in Step 18 a compound of general formula (XXVIII) that can be obtained by the first form of the production process described above may be reacted by the same method as in Step 7 above to obtain a compound represented by general formula (XXIX).

In Step 19, the compound of general formula (XXIX) and hydroxylamine hydrochloride are reacted in the presence or in the absence of a base such as sodium acetate, triethylamine, potassium carbonate, etc. and in the presence or in the absence of an inert solvent such as N,N-dimethylformamide, an alcohol such as methanol, ethanol, etc. or methylene chloride in a range from 0°C to 200°C, to obtain a compound represented by general formula (XXX).

In Step 20, the oxime group of the compound of general formula (XXX) may be reduced by catalytic reduction using an appropriate catalyst, to obtain a compound represented by general formula (XXXI). As examples of appropriate catalysts there may be mentioned platinum, Raney nickel, palladium carbon, etc., and the reaction may be carried out in a solvent of water or an alcoholic solvent such as methanol, ethanol, etc. or a mixture of water and an alcoholic solvent, in the presence or in the absence of ammonia water or ammonia gas under temperature conditions of from room temperature to 200°C and in a pressure range of from normal pressure to 100 atmospheres.

A medicinal agent having as an effective component a novel 1-(substituted aryl)alkyl-1H-imidazopyridine-4-amine derivative represented by general formula (I) above produced in this fashion, or a pharmacologically acceptable salt thereof, is usually administered in the form of an oral preparation such as capsules, tablets, fine particles, granules, powder, syrup, etc. or a parenteral preparation such as an injection, suppository, eye drops, eye ointment, ear drops, external application, etc. These preparations can be produced by common methods with addition of pharmacologically and pharmaceutically acceptable additives. Specifically, for oral preparations and suppositories there may be used formulating components such as excipients (lactose, D-mannitol, corn starch, crystalline cellulose, etc.), disintegrating agents (carboxymethyl cellulose, carboxymethyl cellulose calcium, etc.), binding agents (hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, etc.), lubricating agents (magnesium stearate, talc, etc.), coating agents (hydroxypropylmethyl cellulose, white sugar, titanium oxide, etc.) and bases (polyethylene glycol, hard fat, etc.); for injections or eye drops and ear drops there may be used formulating components such as dissolving agents or dissolving aids which are either aqueous or can form preparations that dissolve upon use (distilled water for injection, physiological saline, propylene glycol, etc.), pH regulators (inorganic or organic acids or bases), isotonizing agents (salt, glucose, glycerin, etc.) and stabilizers; and for eye ointments and external preparations there may be used appropriate formulating components such as ointments, creams and tackifiers (white vaseline, macrogol, glycerin, cotton fabric, etc.)

The dosage of the compounds for patients under treatment will depend on the symptoms of the patients, but the daily dosage for adults is usually about 0.1-1000 mg when administered orally and about 0.01-500 mg when administered parenterally.

[Examples]

The present invention will now be explained by way of reference examples and examples which, however, are in no way intended to restrict the invention.

Reference Example 1

2-[4-(methylamino)phenyl]ethylamine·hydrochloride

(1) N-[4-(cyanomethyl)phenyl]formamide

A mixed solution of 71 ml of acetic anhydride and 40 ml of formic acid was stirred at 50°C for 3 minutes, after which 20.0 g of 4-aminobenzyl cyanide was added while stirring on ice, and the mixture was further stirred at room temperature for 30 minutes. A 20% sodium hydroxide aqueous solution was added to the reaction solution to adjust the liquid to pH 8. After filtering off the precipitated crystals, they were washed with water to obtain 19.0 g of N-[4-(cyanomethyl)phenyl] formamide (melting point: 103.0-105.0°C).

(2) 2-[4-(methylamino)phenyl]ethylamine·hydrochloride

To a suspension of 22.8 g of lithium aluminum hydride and 500 ml of anhydrous tetrahydrofuran under a nitrogen stream there was added dropwise over 30 minutes a mixed solution of 29.5 g of concentrated sulfuric acid and 100 ml of anhydrous tetrahydrofuran, while stirring on ice. After heating the mixture to room temperature, a solution of 19.3 g of N-[4-(cyanomethyl)phenyl]formamide in 400 ml of anhydrous tetrahydrofuran was added dropwise over one hour. After stirring at room temperature for one hour, a mixed solution of 60 ml of water and 120 ml of tetrahydrofuran was added dropwise. After adding 9.5 g of potassium carbonate, the mixture was stirred at room temperature for 14 hours. The insoluble portion was filtered off and washed with tetrahydrofuran and methylene chloride. The filtrate was dried, and then ethanolic hydrogen chloride was added to adjust the liquid to pH 2. The precipitated crystals were filtered off and washed with tetrahydrofuran to obtain 18.9 g of light brown crystals. Recrystallization from ethanol yielded light brown crystals with a melting point of 215.0-220.0°C.

Elemental analysis: $C_9H_{14}N_2 \cdot 2HCL$

Calculated: C, 48.44; H, 7.23; N, 12.55

Found: C, 48.39; H, 7.29; N, 12.59

Reference Example 2

2-[4-(2-aminoethyl)phenyl]-2-methyl-1,3-dioxolane

(1) N-[2-[4-(2-methyl-1,3-dioxolan-2-yl)phenyl]ethyl] trifluoroacetamide

After dissolving 10.0 g of N-[2-(4-acetylphenyl)ethyl] trifluoroacetamide in 100 ml of toluene, 12.0 g of ethylene glycol and 0.4 g of p-toluenesulfonic acid·$1H_2O$ were added and the mixture was refluxed for 15 hours using a Dean Stark apparatus. After cooling the reaction solution, it was washed with water and dewatered, and then the solvent was distilled off under reduced pressure to obtain 11.0 g of N-[2-[4-(2-methyl-1,3-dioxolan-2-yl)phenyl]ethyl] trifluoroacetamide (melting point: 72.0-74.0°C).

(2) 2-[4-(2-aminoethyl)phenyl]-2-methyl-1,3-dioxolane

After dissolving 11.0 g of N-[2-[4-(2-methyl-1,3-dioxolan-2-yl)phenyl]ethyl] trifluoroacetamide in 30 ml of methanol, 20 ml of a 10% sodium hydroxide aqueous solution was added and the mixture was stirred at room temperature for 2 hours. After concentrating the reaction solution under reduced pressure, it was extracted with a mixed solution of methylene chloride and methanol (10:1) and dried, and then the solvent was distilled off under reduced pressure to obtain 7.20 g of a brown liquid.

Mass spectrum m/z: 207 (M^+)

NMR spectrum δ($CDCl_3$) ppm: 1.65(3H, s), 2.74(2H, t, J=6.5Hz), 2.97-3.00(2H, m), 3.79(2H, t, J=2Hz), 4.03(2H, t, J=2Hz), 7.18(2H, d, J=8Hz), 7.41(2H, d, J=8Hz)

Reference Example 3

N-[1-[4-(2-aminoethyl)phenyl]ethyl] acetamide·hydrochloride

(1) N-[1-[4-[2-(tert-butoxycarbonylamino)ethyl]phenyl]ethyl] acetamide

To 10.0 g of [4-[2-(tert-butoxycarbonylamino)ethyl] acetophenone there were added 100 ml of 10% methanolic ammonia and 1 ml of Raney nickel, and the mixture was stirred for 48 hours under a hydrogen atmosphere at 60°C, 80 atmospheres. After cooling the reaction solution, the catalyst was distilled off and the solution was concentrated under reduced pressure. The resulting green liquid was dissolved in 70 ml of methylene chloride, and then 5.8 ml of triethylamine and 3.9 ml of acetic anhydride were added while stirring on ice, and stirring was continued for 30 minutes. After adding water and extracting with methylene chloride, the solution was dried and concentrated under reduced pressure. The residue was washed with diethyl ether to obtain 9.30 g of N-[1-[4-[2-(tert-butoxycarbonylamino) ethyl]phenyl]ethyl] acetamide (melting point: 138.0-140.0°C).

(2) N-[1-[4-(2-aminoethyl)phenyl]ethyl] acetamide·hydrochloride

After dissolving 9.00 g of N-[1-[4-[2-(tert-butoxycarbonylamino)ethyl]phenyl]ethyl] acetamide in 18 ml of methanol, 27 ml of 15% ethyl acetate-containing hydrogen chloride was added and the mixture was stirred at room temperature one hour. After concentrating the reaction solution under reduced pressure, 10 ml of isopropyl alcohol was added, the mixture was stirred on ice, and the precipitated crystals were filtered off to obtain 6.0 g of colorless crystals. Recrystallization from ethanol yielded colorless crystals with a melting point of 212.0-214.0°C.

Elemental analysis: $C_{12}H_{18}N_2O \cdot HCL$

Calculated: C, 59.37; H, 7.89; N, 11.54

Found: C, 59.25; H, 7.61; N, 11.48

Reference Example 4

2-[4-(dibenzylamino)phenyl]ethylamine·hydrochloride

(1) N-[2-[4-(dibenzylamino)phenyl]ethyl] trifluoroacetamide

To 1.00 g of N-[2-(4-aminophenyl)ethyl] trifluoroacetamide there were added 600 mg of potassium carbonate, 10 ml of N,N-dimethylformamide and 1.1 ml of benzyl bromide, and the mixture was stirred at 50°C for one hour. After adding water and extracting with diethyl ether, the solution was dried and concentrated under reduced pressure. The residue was washed with isopropyl ether to obtain 1.10 g of N-[2-[4-(dibenzylamino)phenyl]ethyl] trifluoroacetamide (melting point: 142.0-144.0°C).

(2) 2-[4-(dibenzylamino)phenyl]ethylamine·hydrochloride

To 1.00 g of N-[2-[4-(dibenzylamino)phenyl]ethyl] trifluoroacetamide there were added 3 ml of methanol and 2 ml of a 10% sodium hydroxide aqueous solution, and the mixture was stirred at 60°C for 30 minutes. After concentrating the reaction solution under reduced pressure, water was added and the solution was extracted with methylene chloride and dried. Ethanolic hydrogen chloride was added to the methylene chloride layer, and after stirring on ice the precipitated crystals were filtered off to obtain 1.00 g of colorless crystals. Recrystallization from a mixed solution of methylene chloride and ethanol yielded colorless crystals with a melting point of 168.0-170.0°C.

Elemental analysis: $C_{22}H_{24}N_2\cdot 2HCl\cdot 1/4H_2O$
Calculated: C, 67.09; H, 6.78; N, 7.11
Found: C, 67.01; H, 6.81; N, 7.23

Reference Example 5

4-(2-aminoethyl)-α-methylbenzyl alcohol·hydrochloride

After dissolving 10.0 g of 4-(2-azidoethyl) acetophenone in 50 ml of methanol, 2.0 g of sodium borohydride was added and the mixture was stirred at room temperature for one hour. After concentrating the reaction solution under reduced pressure, water was added and the solution was extracted with diethyl ether, dried and then concentrated under reduced pressure. The resulting faint yellow liquid was dissolved in 150 ml of tetrahydrofuran, and after adding 21.7 g of triphenylphosphine and 2.5 ml of water, the mixture was stirred at room temperature for 10 hours. After concentrating the reaction solution under reduced pressure, it was dissolved in 100 ml of ethanol, and then ethanolic hydrogen chloride was added prior to stirring on ice. The precipitated crystals were filtered off to obtain 9.00 g of colorless crystals. Recrystallization from ethanol yielded colorless crystals with a melting point of 171.0-172.0°C.

Elemental analysis: $C_{10}H_{15}NO \cdot HCl$
Calculated: C, 59.55; H, 8.00; N, 6.94
Found: C, 59.29; H, 8.27; N, 6.85

Reference Example 6

4-(3-aminopropyl)benzenesulfonamide·hydrochloride

(1) N-(3-phenylpropyl)acetamide

To a solution of 1.00 g of 3-phenylpropylamine in 25 ml of pyridine there was added dropwise 3.8 ml of acetic anhydride while cooling on ice, and then the mixture was stirred at room temperature for one hour. The solvent was distilled off under reduced pressure, ethyl acetate and 10% hydrochloric acid were added to the residue, and after adjusting the liquid to pH 3-4 it was separated. After washing, the organic layer with water and then with saturated saline and dewatering, the solvent was distilled off under reduced pressure to obtain 6.20 g of N-(3-phenylpropyl)acetamide.

(2) 4-[3-(acetylamino)propyl]benzenesulfonyl chloride

To a solution of 1.00 g of N-(3-phenylpropyl)acetamide in 10 ml of methylene chloride there was added dropwise 3.40 g of chlorsulfonic acid while cooling on ice, after which the mixture was refluxed for one hour. The reaction mixture was poured into ice water, and the separated organic layer was washed with saturated saline. After dewatering the organic layer, the solvent was distilled off under reduced pressure to obtain 1.20 g of 4-[3-(acetylamino)propyl]benzenesulfonyl chloride.

(3) 4-[3-(acetylamino)propyl]benzenesulfonamide

A mixture of 1.20 g of 4-[3-(acetylamino)propyl] benzenesulfonyl chloride, 6 ml of tetrahydrofuran and 3.0 g of ammonia water was stirred at room temperature for 7 hours. After distilling off the solvent under reduced pressure and adding methanol to the residue, the insoluble portion was filtered off. The filtrate was concentrated to obtain 0.50 g of 4-[3-(acetylamino)propyl]benzenesulfonamide.

(4) 4-(3-aminopropyl)benzenesulfonamide·hydrochloride

A mixture of 1.95 g of 4-[3-(acetylamino)propyl] benzenesulfonamide and 20 ml of 6 N hydrochloric acid was stirred at 110-120°C for 6 hours. The reaction mixture was concentrated under reduced pressure, and the residue was washed with ethanol to obtain 0.95 g of colorless crystals.

NMR spectrum δ (DMSO) ppm: 1.89(2H, quint, J=8Hz), 2.74(2H, t, J=8Hz), 2.80(2H, t, J=8Hz), 7.20(2H, br-s), 7.40(2H, d, J=8.5Hz), 7.76(2H, d, J=8.5Hz), 7.93(2H, br-s)

Reference Example 7

N-[4-(2-aminoethyl)phenyl]-4-methylbenzenesulfonamide

(1) N-[2-(4-nitrophenyl)ethyl] trifluoroacetamide

To a mixture of 5.00 g of 2-(4-nitrophenyl)ethylamine·hydrochloride and 50 ml of methylene chloride there were added 3.4 ml of triethylamine and 10.5 ml of trifluoroacetic anhydride while cooling on ice, and the mixture was stirred at room temperature for 30 minutes. After concentrating the reaction mixture under reduced pressure and adding water to the residue, extraction was performed with methylene chloride. After washing the extract with saturated saline and dewatering, the solvent was distilled off under reduced pressure to obtain 8.50 g of N-[2-(4-nitrophenyl)ethyl] trifluoroacetamide.

(2) N-[2-(4-aminophenyl)ethyl] trifluoroacetamide

After dissolving 36.3 g of N-[2-(4-nitrophenyl)ethyl] trifluoroacetamide in 180 ml of methanol, 1.8 g of 5% palladium-carbon was added and the solution was subjected to catalytic reduction at normal temperature and normal pressure for 17 hours. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to obtain 33.4 g of N-[2-(4-aminophenyl)ethyl] trifluoroacetamide.

(3) N-[4-[2-(trifluoroacetylamino)ethyl]phenyl]-4-methylbenzenesulfonamide

To a mixture of 10.0 g of N-[2-(4-amin phenyl)ethyl] trifluoroacetamide, 50 ml of methylene chloride and 7.9 ml of triethylamine there was added dropwise a 10-ml solution of methylene chloride containing 10.8 g of p-toluenesulfonyl chloride while stirring on ice, and the stirring was continued for one hour. Water was added to the reaction mixture, and the precipitated crystals were filtered off to obtain 10.7 g of N-[4-[2-(trifluoroacetylamino)ethyl]phenyl]-4-methylbenzenesulfonamide.

(4) N-[4-(2-aminoethyl)phenyl]-4-methylbenzenesulfonamide

A mixture of 13.4 g of N-[4-[2-(trifluoroacetylamino)ethyl] phenyl]-4-methylbenzenesulfonamide, 130 ml of methanol and 80 ml of a 10% sodium hydroxide aqueous solution was stirred at room temperature for 30 minutes. After adding 10% hydrochloric acid to the reaction mixture to adjust the liquid to pH 7, it was concentrated under reduced pressure. After adding ethanol to the residue and filtering off the insoluble portion, the filtrate was concentrated under reduced pressure to obtain 12.0 g of a light yellow liquid.

NMR spectrum δ(DMSO) ppm: 2.33(3H, s), 2.76(2H, t, J=8.5Hz), 2.96(2H, t, J=8.5Hz), 7.05(2H, d, J=8.5Hz), 7.10(2H, d, J=8.5Hz), 7.34(2H, d, J=8Hz), 7.65(2H, d, J=8Hz), 8.40(2H, br-s)

Reference Example 8

4-(2-aminoethyl)-N-methylbenzenesulfonamide·hydrochloride

(1) N-(2-phenylethyl)acetamide

To a solution of 15.0 g of 2-phenylethylamine in 75 ml of pyridine there was added dropwise 12.8 ml of acetic anhydride while cooling on ice, and the mixture was stirred at room temperature for one hour. After concentrating the reaction mixture under reduced pressure and adding 10% hydrochloric acid to the residue to adjust the liquid to pH 3-4, extraction was performed with ethyl acetate. The extract was washed with water and then with saturated saline and dewatered, and the solvent was distilled off under reduced pressure to obtain 27.7 g of N-

'(2-phenylethyl)acetamide.

(2) 4-[2-(acetylamino)ethyl]benzenesulfonyl chloride

To a mixed solution of 98.2 g of N-(2-phenylethyl)acetamide and 500 ml of methylene chloride there was added dropwise 362 g of chlorsulfonic acid while cooling on ice. After refluxing for 2 hours, the reaction solution was poured into ice water. The precipitated crystals were filtered off and then washed with water to obtain 88.3 g of 4-[2-(acetylamino)ethyl] benzenesulfonyl chloride.

(3) 4-[2-(acetylamino)ethyl]-N-methylbenzenesulfonamide

To a solution of 5.00 g of 4-[2-(acetylamino)ethyl] benzenesulfonyl chloride in 25 ml of tetrahydrofuran there was added at room temperature 14.8 g of a 40% methylamine aqueous solution. After refluxing for 5 hours, the mixture was concentrated under reduced pressure to obtain 5.90 g of 4-[2-(acetylamino)ethyl]-N-methylbenzenesulfonamide.

(4) 4-(2-aminoethyl)-N-methylbenzenesulfonamide·hydrochloride

A mixture of 34.0 g of 4-[2-(acetylamino)ethyl]-N-methylbenzenesulfonamide and 170 ml of 6 N hydrochloric acid was stirred at 110°C for 5 hours. The reaction mixture was concentrated under reduced pressure and the residue was washed with methanol to obtain 10.6 g of colorless crystals.

NMR spectrum δ(DMSO) ppm: 2.42(3H, s), 3.02(2H, t, J=5Hz), 3.07(2H, t, J=5Hz), 7.40(1H, br-s), 7.57(2H, d, J=8Hz), 7.74(2H, d, J=8Hz), 8.08(2H, br-s)

Reference Example 9

4-(2-aminoethyl)-N-propylbenzenesulfonamide

(1) N-propyl-4-[2-(trifluoroacetylamino)ethyl] benzenesulfonamide

To a solution of 13.4 g of 4-[2-(trifluoroacetylamino) ethyl]benzenesulfonyl chloride in 20 ml of tetrahydrofuran there was added 6.9 ml of propylamine while cooling on ice, and the mixture was stirred on ice for 3 hours. The reaction mixture was concentrated under reduced pressure, and water and methylene chloride were added to the residue. The precipitated crystals were filtered off to obtain 15.3 g of N-propyl-4-[2-

(trifluoroacetylamino)ethyl]benzenesulfonamide.

(2) 4-(2-aminoethyl)-N-propylbenzenesulfonamide

To a solution of 15.3 g of N-propyl-4-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide in 150 ml of methanol there was added at room temperature 92 ml of a 10% sodium hydroxide aqueous solution, and the mixture was stirred for 30 minutes. After adding 10% hydrochloric acid to the reaction mixture to adjust the liquid to pH 7-8, it was concentrated under reduced pressure. After adding ethanol to the residue and filtering off the insoluble portion, the filtrate was concentrated under reduced pressure to obtain 12.7 g of a colorless liquid.

NMR spectrum δ(DMSO) ppm: 0.80(3H, t, J=7Hz), 1.40(2H, sextet, J=7Hz), 2.70(2H, t, J=7Hz), 2.97(2H, t, J=7.5Hz), 3.09(2H, t, J=7.5Hz), 4.23(1H, br-s), 7.46(2H, d, J=8Hz), 7.74(2H, d, J=8Hz), 7.80-8.00(2H, br-s)

Reference Example 10

4-(2-aminoethyl)-N, N-dimethylbenzenesulfonamide·hydrochloride

(1) 4-[2-(acetylamino)ethyl]-N,N-dimethylbenzenesulfonamide

To a solution of 5.00 g of 4-[2-(acetylamino)ethyl]benzenesulfonyl chloride in 25 ml of tetrahydrofuran there was added at room temperature 17.2 g of a 50% dimethylamine aqueous solution, and the mixture was refluxed for 5 hours. The reaction mixture was concentrated under reduced pressure to obtain 4.10 g of 4-[2-(acetylamino)ethyl]-N,N-dimethylbenzenesulfonamide.

(2) 4-(2-aminoethyl)-N,N-dimethylbenzenesulfonamide·hydrochloride

A mixture of 4.10 g of 4-[2-(acetylamino)ethyl]-N,N-dimethylbenzenesulfonamide and 40 ml of 6 N hydrochloric acid was stirred at 100°C for 6 hours. The reaction mixture was concentrated under reduced pressure and the residue was washed with methanol to obtain 1.00 g of colorless crystals.

NMR spectrum δ(DMSO) ppm: 2.62(6H, s), 3.01(2H, t, J=8.5Hz), 3.11(2H, t, J=8.5Hz), 7.54(2H, d, J=8Hz), 7.70(2H, d, J=8Hz), 8.00(2H, br-s)

Reference Example 11

2-(2-aminoethyl)benzenesulfonamide

(1) 5-bromo-2-[2-(trifluoroacetylamino)ethyl]benzenesulfonyl chloride

To a solution of 15.5 g of N-[2-(4-bromophenyl)ethyl] trifluoroacetamide in 45 ml of methylene chloride there was added 10 ml of chlorsulfonic acid while cooling on ice, and the mixture was refluxed for two days. After pouring the reaction mixture into ice water for separation, the organic layer was washed first with water and then with saturated saline. After dewatering the organic layer, the solvent was distilled off under reduced pressure. A mixture of n-hexane and ethyl acetate (6:1) was added to the residue, and the insoluble portion was filtered off. After concentrating the filtrate under reduced pressure, the residue was purified by column chromatography [silica gel, n-hexane/ethyl acetate (6:1)] to obtain 4.90 g of 5-bromo-2-[2-(trifluoroacetylamino)ethyl]benzenesulfonyl chloride.

(2) 5-bromo-2-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide

To a solution of 25.5 g of 5-bromo-2-[2-(trifluoroacetylamino)ethyl]benzenesulfonyl chloride in 38 ml of tetrahydrofuran there was added 45 ml of ammonia water while cooling on ice, and the mixture was stirred at room temperature for one hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with methylene chloride to obtain 22.0 g of 5-bromo-2-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide.

(3) 2-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide

A mixture of 12.0 g of 5-bromo-2-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide, 120 ml of methanol and 1.2 g of 10% palladium-carbon was subjected to catalytic reduction at normal temperature and normal pressure for 4 hours. After filtering off the catalyst, the filtrate was concentrated under reduced pressure to obtain 11.0 g of 2-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide.

(4) 2-(2-aminoethyl)benzenesulfonamide

A mixture of 11.0 g of 2-[2-(trifluoroacetylamino)ethyl] benzenesulfonamide, 110 ml of methanol and 66 ml of a 10% sodium hydroxide aqueous solution was stirred at room temperature for one hour. After adding 10% hydrochloric acid to the reaction mixture to adjust the liquid to pH 7-8, it was concentrated under reduced pressure. After adding ethanol to the residue and filtering off the insoluble portion, the filtrate was distilled off under reduced pressure to obtain 8.0 g of colorless crystals. NMR spectrum δ (DMSO) ppm: 3.10(2H, t, J=7Hz), 3.30(2H, t, J=7Hz), 7.43-7.47(2H, m), 7.50-7.60(5H, m), 7.90-7.93(1H, m)

Reference Example 12

3-(2-aminoethyl)benzenesulfonamide

(1) N-[2-(4-bromophenyl)ethyl]trifluoroacetamide

To a solution of 10.0 g of 2-(4-bromophenyl)ethylamine in 100 ml of methylene chloride there was added 21 ml of trifluoroacetic anhydride while cooling on ice, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure and the residue was washed with isopropyl ether to obtain 13.7 g of N-[2-(4-bromophenyl)ethyl]trifluoroacetamide.

(2) 2-bromo-5-[2-(trifluoroacetylamino)ethyl] benzenesulfonyl chloride

To a solution of 15.3 g of N-[2-(4-bromophenyl)ethyl]trifluoroacetamide in 45 ml of methylene chloride there was added 10 ml of chlorsulfonic acid while cooling on ice, and the mixture was refluxed for two days. After pouring the reaction mixture into ice water for separation, the organic layer was washed first with water and then with saturated saline. After dewatering the organic layer, the solvent was distilled off under reduced pressure. The residue was washed with a mixed solution of n-hexane and ethyl acetate (6:1) to obtain 8.20 g of 2-bromo-5-[2-(trifluoroacetylamino)ethyl]benzenesulfonyl chloride.

(3) 2-bromo-5-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide

To a solution of 8.20 g of 2-bromo-5-[2-(trifluoroacetylamino)ethyl]benzenesulfonyl chloride in 12 ml of tetrahydrofuran there was added 14.4. ml of ammonia water while cooling on ice, and the mixture was stirred at room temperature for one hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with ethanol t obtain 5.30 g of 2-bromo-5-[2-(trifluoroacetylamino)ethyl] benzenesulfonamide.

(4) 3-[2-(trifluoroacetylamino)ethyl]benzenesulfonamide

A mixture of 5.30 g of 2-bromo-5-[2-(trifluoroacetylamino) ethyl]benzenesulfonamide, 50 ml of methanol and 0.5 g of 10% palladium-carbon was subjected to catalytic reduction at normal temperature and normal pressure for 11 hours. After filtering off the catalyst, the filtrated was concentrated under reduced pressure to obtain 4.00 g of 3-[2-(trifluoroacetylamino)ethyl] benzenesulfonamide.

(5) 3-(2-aminoethyl)benzenesulfonamide

A mixture of 4.00 g of 3-[2-(trifluoroacetylamino)ethyl] benzenesulfonamide, 40 ml of methanol and 24 ml of a 10% sodium hydroxide aqueous solution was stirred at room temperature for 3 hours. After adding 10% hydrochloric acid to the reaction mixture to adjust the liquid to pH 7-8, it was concentrated under reduced pressure. After adding ethanol to the residue and filtering off the insoluble portion, the filtrate was concentrated under reduced pressure to obtain 4.30 g of colorless crystals.

NMR spectrum δ(DMSO) ppm: 2.98(2H, t, J=8Hz), 3.08(2H, t, J=8Hz), 7.25(2H, br-s), 7.48-7.58(2H, m), 7.70-7.78(2H, m), 7.81(2H, br-s)

Reference Example 13

4-[2-[(2-chloro-3-nitroquinolin-4-yl)amino]ethyl]benzamide

To a solution of 8.03 g of 2,4-dichloro-3-nitroquinoline and 18.5 ml of triethylamine in N,N-dimethylformamide there was added 4.35 g of 4-(2-aminoethyl)benzamide while stirring on ice, and the mixture was further stirred on ice for 5 hours. After adding water and 10% hydrochloric acid to the reaction solution to adjust the liquid to pH 8, extraction was performed with ethyl acetate. The organic layer was washed with saturated saline and then dewatered, and the solvent was distilled off under reduced pressure. The residue was washed with isopropyl ether to obtain 5.89 g of brown crystals. Recrystallization from ethanol yielded yellowish brown prism crystals with a melting point of 217.5-218.5°C.

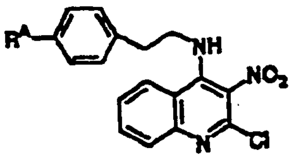
Elemental analysis: $C_{18}H_{15}ClN_4O_3$

Calculated: C, 58.31; H, 4.08; N, 15.11

Found: C, 58.32; H, 3.88; N, 15.04

The compounds for Reference Examples 14-46 listed in Tables 1 to 9 were obtained according to the method of Reference Example 13.

Table 1



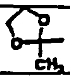
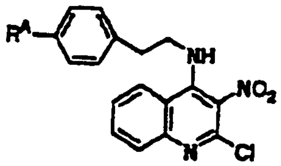
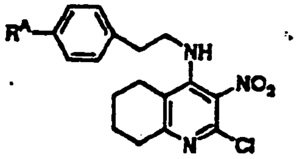
	R^A	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.14	CONHMe	yellowish brown crystals (EtOH) mp: 194.0-196.0°C	$C_{19}H_{17}ClN_4O_3$ Calc.: C,59.30; H,4.45; N,14.56 Found: C,59.30; H,4.59; N,14.29
Ref. Ex.15	OH	yellowish brown crystals (AcOEt) mp: 140.0-145.0°C, decomposition	$C_{17}H_{14}ClN_3O_3$ Calc.: C,59.40; H,4.10; N,12.22 Found: C,59.32; H,3.83; N,12.20
Ref. Ex.16	CO_2Et	orange needle-like crystals (EtOH) mp: 122.0-124.0°C	$C_{20}H_{18}ClN_3O_4$ Calc.: C,60.08; H,4.54; N,10.51 Found: C,60.15; H,4.32; N,10.56
Ref. Ex.17		yellow crystals (Et_2O) mp: 122.5-123.0°C	$C_{21}H_{20}ClN_3O_4$ Calc.: C,60.95; H,4.87; N,10.15 Found: C,60.83; H,4.77; N,10.19
Ref. Ex.18	SO_2NH_2	yellow crystals ($DMF-H_2O$) mp: 199.5-201.5°C	$C_{17}H_{15}ClN_4O_4S$ Calc.: C,50.19; H,3.72; N,13.77 Found: C,49.99; H,3.56; N,13.48
Ref. Ex.19	SO_2NHMe	yellow needle-like crystals (CH_3CN) mp: 178.0-179.0°C	$C_{18}H_{17}ClN_4O_4S$ Calc.: C,51.37; H,4.07; N,13.31 Found: C,51.46; H,3.96; N,13.47
Ref. Ex.20	SO_2NHEt	light yellow needle-like crystals (EtOH) mp: 183.0-184.5°C	$C_{19}H_{19}ClN_4O_4S$ Calc.: C,52.47; H,4.40; N,12.88 Found: C,52.78; H,4.34; N,12.77
Ref. Ex.21	SO_2NH-n-Pr	brown needle-like crystals (iso-PrOH) mp: 136.0-137.5°C	$C_{20}H_{21}ClN_4O_4S$ Calc.: C,53.51; H,4.71; N,12.48 Found: C,53.80; H,4.70; N,12.63
Ref. Ex.22	SO_2NMe_2	yellow needle-like crystals (CH_3CN) mp: 162.0-163.0°C	$C_{19}H_{19}ClN_4O_4S$ Calc.: C,52.47; H,4.40; N,12.88 Found: C,52.57; H,4.30; N,13.13
Ref. Ex.23	CH_2OH	yellow crystals (iso-PrOH) mp: 169.0-171.0°C	$C_{18}H_{16}ClN_3O_3$ Calc.: C,60.42; H,4.51; N,11.74 Found: C,60.72; H,4.23; N,11.71
Ref. Ex.24	NHMs	yellow crystals ($DMF-H_2O$) mp: 210.5-213.0°C	$C_{18}H_{17}ClN_4O_4S$ Calc.: C,51.37; H,4.07; N,13.31 Found: C,51.39; H,4.02; N,13.14
Ref. Ex.25	NHAc	yellow crystals (EtOH) mp: 190.0-191.5°C	$C_{19}H_{17}ClN_4O_3$ Calc.: C,59.30; H,4.45; N,14.56 Found: C,59.28; H,4.37; N,14.59

Table 2



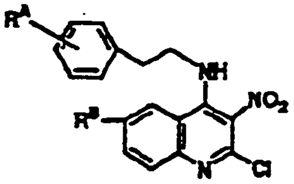
	R^A	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.26	NHMe	yellow prism crystals (AcOEt) mp: 146.5-147.5°C	$C_{18}H_{17}ClN_4O_2$ Calc.: C,60.59; H,4.80; N,15.70 Found: C,60.75; H,4.69; N,15.66
Ref. Ex.27	CHMeNHAc	yellow crystals (AcOEt) mp: 192.5-194.0°C	$C_{21}H_{21}ClN_4O_3$ Calc.: C,61.09; H,5.13; N,13.57 Found: C,61.06; H,5.22; N,13.37

Table 3



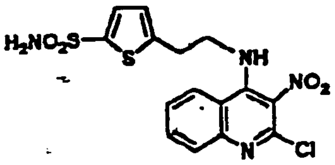
	R^A	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.28	SO_2NH_2	yellow crystals (MeOH) mp: 194.0-196.0°C	$C_{17}H_{19}ClN_4O_4S$ Calc.: C,49.69; H,4.66; N,13.64 Found: C,49.55; H,4.76; N,13.52
Ref. Ex.29	CH_2OH	yellow crystals (iso-PrOH) mp: 149.5-151.0°C	$C_{18}H_{20}ClN_3O_3$ Calc.: C,59.75; H,5.57; N,11.61 Found: C,59.65; H,5.38; N,11.53
Ref. Ex.30	NHMs	yellow crystals (AcOEt-iso-Pr_2O) mp: 176.5-177.5°C	$C_{18}H_{21}ClN_4O_4S$ Calc.: C,50.88; H,4.98; N,13.19 Found: C,50.89; H,4.97; N,13.04
Ref. Ex.31	NHAc	yellow prism crystals (AcOEt) mp: 187.5-188.5°C	$C_{19}H_{21}ClN_4O_3$ Calc.: C,58.69; H,5.44; N,14.41 Found: C,58.64; H,5.45; N,14.30
Ref. Ex.32	NHMe	yellowish brown needle-like crystals (AcOEt) mp: 146.5-148.0°C	$C_{18}H_{21}ClN_4O_2$ Calc.: C,59.91; H,5.87; N,15.53 Found: C,59.86; H,5.73; N,15.59
Ref. Ex.33	CHMeNHAc	yellow crystals (AcOEt) mp: 170.0-174.0°C	$C_{21}H_{25}ClN_4O_3$ Calc.: C,60.50; H,6.04; N,13.44 Found; C,60.39; H,6.10; N,13.24

Table 4



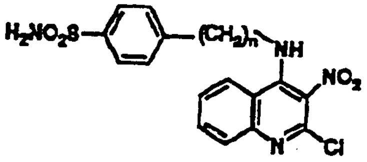
	R^A	R^B	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.34	o-SO_2NH_2	H	yellow needle-like crystals (CH_3CN) mp: 232.0-233.0°C	$C_{17}H_{15}ClN_4O_4S$ Calc.: C,50.19; H,3.72; N,13.77 Found: C,50.19; H,3.55; N,13.72
Ref. Ex.35	m-SO_2NH_2	H	yellowish brown crystals (CH_3CN) mp: 225.5-226.5°C	$C_{17}H_{15}ClN_4O_4S$ Calc.: C,50.19; H,3.72; N,13.77 Found: C,50.11; H,3.55; N,13.59
Ref. Ex.36	p-SO_2NH_2	Me	yellowish brown crystals (EtOH) mp: 235.5-237.0°C	$C_{18}H_{17}ClN_4O_4S$ Calc.: C,51.37; H,4.07; N,13.31 Found: C,51.49; H,4.07; N,13.03
Ref. Ex.37	p-SO_2NH_2	OMe	yellowish brown needle-like crystals (EtOH) mp: 238.0-239.5°C	$C_{18}H_{17}ClN_4O_5S$ Calc.: C,49.49; H,3.92; N,12.82 Found: C,49.44; H,3.79; N,12.90
Ref. Ex.38	p-SO_2NH_2	Cl	yellow crystals (EtOH) mp: 236.0-237.0°C	$C_{17}H_{14}Cl_2N_4O_4S$ Calc.: C,46.27; H,3.20; N,12.70 Found: C,46.29; H,3.07; N,12.54

Table 5



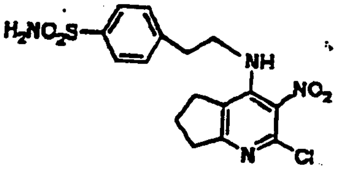
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.39	yellow crystals (EtOH) mp: 196.5-197.5°C	$C_{15}H_{13}ClN_4O_4S_2$ Calc.: C,43.64; H,3.17; N,13.57 Found: C,43.75; H,3.06; N,13.33

Table 6



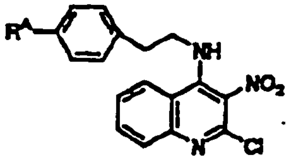
	n	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.40	1	yellow needle-like crystals (EtOH) mp: 212.0-213.0°C, decomposition	$C_{16}H_{13}ClN_4O_4S$ Calc.: C,48.92; H,3.34; N,14.26 Found: C,49.18; H,3.26; N,14.33
Ref. Ex.41	3	yellow plate crystals (CH_3CN) mp: 215.0-216.0°C	$C_{18}H_{17}ClN_4O_4S$ Calc.: C,51.37; H,4.07; N,13.31 Found: C,51.25; H,4.09; N,13.02

Table 7



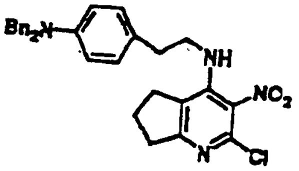
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.42	yellow crystals (MeOH) mp: 216.0-217.0°C	$C_{16}H_{17}ClN_4O_4S$ Calc.: C,48.32; H,4.32; N,14.12 Found: C,48.29; H,4.20; N,14.10

Table 8



	R^A	Properties
Ref. Ex.43	NHTs	yellowish brown liquid NMR spectrum δ (DMSO-d_6) ppm: 2.32(3H, s), 2.84(2H, t, J=8Hz), 3.28(2H, q, J=8Hz), 6.99(2H, d, J=8.5Hz), 7.07(2H, d, J=8.5Hz), 7.27(2H, d, J=8Hz), 7.58(2H, d, J=8Hz), 7.60-7.65(1H, m), 7.80-7.85(3H, m), 8.36(1H, d, J=8.5Hz), 9.98(1H, s) IR spectrum V(liq) cm^{-1}: 3416, 1528, 1160
Ref. Ex.44	NBn_2	reddish brown liquid NMR spectrum δ ($CDCl_3$) ppm: 2.89(2H, t, J=6.5Hz), 3.61(2H, q, J=6.5Hz), 4.66(4H, s), 5.84(1H, t, J=6.5Hz), 6.73(2H, d, J=8Hz), 7.04(2H, d, J=8Hz), 7.20-7.35(10H, m), 7.40(1H, t, J=8Hz), 7.61(1H, d, J=8Hz), 7.71(1H, t, J=8Hz), 7.89(1H, d, J=8Hz) Mass spectrum m/z: 522, 524(3:1, M^+) IR spectrum V(liq) cm^{-1}: 3416, 1522
Ref. Ex.45	CHMeOH	yellow crystals NMR spectrum δ ($CDCl_3$) ppm: 1.50(3H, d, J=6Hz), 3.00(2H, t, J=7Hz), 3.73(2H, q, J=7Hz), 4.92(1H, q, J=6Hz), 5.86(1H, s), 7.23(2H, d, J=8Hz), 7.38(2H, d, J=8Hz), 7.45-7.50(1H, m), 7.65-7.75(2H, m), 7.89(1H, d, J=8.5Hz) IR spectrum V(KBr) cm^{-1}: 3424, 1516, 1364 Mass spectrum m/z: 370, 372(3:1, M^+)

Table 9



	Properties
Ref. Ex.46	orange liquid NMR spectrum δ($CDCl_3$) ppm: 2.09(2H, quintet, J=7.5Hz), 2.73(2H, t, J=7Hz), 2.89(2H, t, J=7.5Hz), 2.95(2H, t, J=7.5Hz), 3.58(2H, q, J=7Hz), 4.64(4H, s), 5.52(1H, br-s), 6.69(2H, d, J=8.5Hz), 6.94(2H, d, J=8.5Hz), 7.20-7.30(6H, m), 7.33(4H, m) IR spectrum ν(liq) cm^{-1}: 3392, 1522 Mass spectrum m/z: 512, 514(3:1, M^+)

Reference Example 47

N-[4-[2-[(2-chloro-3-nitroquinolin-4-yl)amino]ethyl]phenyl]-N-methylacetamide

To 2.59 g of 2-chloro-N-[2-[4-(methylamino)phenyl]ethyl]-3-nitroquinoline-4-amine there were added 26 ml of pyridine and 6.9 ml of acetic anhydride, and the mixture was stirred at room temperature for 1.5 hours. The solvent was distilled off under reduced pressure and the residue was washed with isopropyl ether to obtain 2.72 g of yellow crystals. Recrystallization from ethanol yielded yellow prism crystals with a melting point of 176.5-177.0°C.

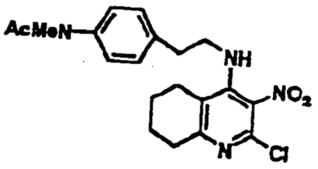
Elemental analysis: $C_{20}H_{19}ClN_4O_3$

Calculated: C, 60.23; H, 4.80; N, 14.05

Found: C, 60.28; H, 4.70; N, 14.01

The compound for Reference Example 48 listed in Table 10 was obtained by the same method as Reference Example 47.

Table 10



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.48	yellow prism crystals (THP) mp: 171.0-172.5°C	$C_{20}H_{23}ClN_4O_3$ Calc.: C,59.63; H,5.75; N,13.91 Pound: C,59.50; H,5.63; N,13.95

Reference Example 49

2-chloro-5,6,7,8-tetrahydro-N-[2-[4-(N-methylbenzylamino)phenyl]ethyl]-3-nitroquinoline-4-amine

To a suspension of 36.8 g of 2-chloro-5,6,7,8-tetrahydro-N-[2-[4-(methylamino)phenyl]ethyl]-3-nitroquinoline-4-amine, 14.1 g of potassium carbonate and 370 ml of N,N-dimethylformamide there was added dropwise 12.4 ml of benzyl bromide at room temperature while stirring. After stirring at room temperature for 14 hours, the reaction mixture was added to ice water and extracted with methylene chloride. The extract was washed with water and then dewatered and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, methylene chloride/n-hexane (1:1)] to obtain 41.9 g of a red liquid.

IR spectrum ν(liq) cm^{-1} : 3432, 1580, 1522

Mass spectrum m/z : 450, 452(M^+, 3:1), 210(BP)

NMR spectrum δ ($CDCl_3$) ppm : 1.65-1.80(4H, m), 2.02-2.15(2H, m), 2.70-2.85(4H, m), 3.03(3H, s), 3.30(2H, q, J=6Hz), 4.33(1H, br-s), 4.53(2H, s), 6.71(2H, d, J=8.5Hz), 7.01(2H, d, J=8.5Hz), 7.15-7.38(5H, m), 7.22(2H, d, J=7.5Hz), 7.24(1H, t, J=7.5Hz), 7.31(2H, t, J=7.5Hz)

Reference Example 50

N-[4-[2-[(2-dibenzylamino-3-nitroquinolin-4-yl)amino]ethyl]phenyl]acetamide

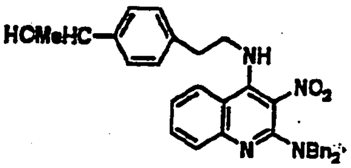
A mixture of 5.75 g of N-[4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl]phenyl]acetamide and 11.9 ml of dibenzylamine was stirred at 100°C for 10 hours. Water and 10% hydrochloric acid were added to the reaction mixture, the precipitate was filtered off, and the mother liquor was extracted with methylene chloride. The extract was washed with water and then dewatered, and the solvent was distilled off. The resulting reddish orange oily residue was purified by column chromatography [silica gel, ethyl acetate/n-hexane (1:2-2:1)] to obtain 6.37 g of a reddish orange liquid.

IR spectrum ν(liq) cm^{-1} : 3320, 1668, 1522

NMR spectrum δ ($CDCl_3$) ppm : 2.15(3H, s), 2.88(2H, t, J=7Hz), 4.03(2H, q, J=7Hz), 4.50(4H, s), 7.00-7.30(13H, m), 7.42(2H, d, J=8Hz), 7.50-7.60(3H, m), 7.92(1H, d, J=8Hz)

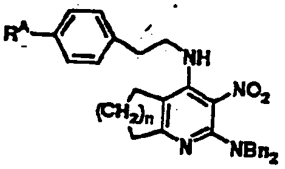
The compounds for Reference Examples 51-54 listed in Tables 11 and 12 were obtained by the same method as Reference Example 50.

Table 11



	Properties
Ref. Ex.51	reddish orange liquid NMR spectrum δ ($CDCl_3$) ppm: 1.48(3H, d, J=6.5Hz), 1.78(1H, br-s), 2.91(2H, t, J=7Hz), 3.96(2H, q, J=7Hz), 4.50(4H, s), 4.86(1H, q, J=6.5Hz), 7.10-7.35(14H, m), 7.50-7.60(3H, m), 7.92(1H, d, J=8Hz) IR spectrum V(liq) cm^{-1}: 3352, 1526 Mass spectrum m/z: 532(M^+)

Table 12



	R^A	n	Properties
Ref. Ex.52	NHAc	2	orange liquid NMR spectrum δ ($CDCl_3$) ppm: 1.65-1.85(4H, m), 2.16(3H, s), 2.30-2.50(2H, m), 2.60-2.75(2H, m), 2.77(2H, t, J=7Hz), 3.45(2H, td, J=7, 6Hz), 4.34(4H, s), 5.78(1H, t, J=6Hz), 7.11(2H, d, J=8.5Hz), 7.15-7.30(10H, m), 7.41(2H, d, J=8.5Hz) IR spectrum V(liq) cm^{-1}: 3316, 1670, 1518
Ref. Ex.53	SO_2NH_2	1	reddish orange liquid NMR spectrum δ (DMSO-d_6) ppm: 1.95-2.05(2H, m), 2.68(2H, t, J=8Hz), 2.88(2H, t, J=7Hz), 3.00(2H, t, J=7Hz), 3.65(2H, td, J=7, 6Hz), 4.34(4H, s), 6.98(1H, t, J=6Hz), 7.10-7.30(12H, m), 7.38(2H, d, J=8Hz), 7.74(2H, d, J=8Hz) IR spectrum V(liq) cm^{-1}: 3352, 1560, 1336
Ref. Ex.54	NBn_2	1	reddish orange liquid

			NMR spectrum δ (CDCl$_3$) ppm: 2.04(2H, quintet, J=7.5Hz), 2.75(2H, t, J=7Hz), 2.76(2H, t, J=7.5Hz), 3.08(2H, t, J=7.5Hz), 3.69(2H, q, J=7Hz), 4.40(4H, s), 4.63(4H, s), 6.68(2H, d, J=8.5Hz), 6.99(2H, d, J=8.5Hz), 7.12(4H, d, J=8Hz), 7.20-7.30(12H, m), 7.32(4H, t, J=8Hz) IR spectrum V(liq) cm^{-1}: 3344, 1522 Mass spectrum m/z: 673(M$^+$)

Reference Example 55

4-[2-[(2-N-methylbenzylamino-3-nitroquinolin-4-yl)amino]ethyl] benzenesulfonamide

After dissolving 2.41 g of 4-[2-[(2-chloro-3-nitroquinolin-4-yl)amino]ethyl] benzenesulfonamide in 7.6 ml of N-methylbenzylamine, the solution was stirred at 100°C for one hour. After cooling the reaction mixture to room temperature, 5% hydrochloric acid was added and extraction was performed with methylene chloride. After washing the extract first with water and then with saturated saline and dewatering, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography [silica gel, methylene chloride/ethanol (50:1-40:1)] to obtain 2.34 g of reddish orange crystals. Recrystallization from methanol yielded reddish orange crystals with a melting point of 156.0-157.5°C.

Elemental analysis: $C_{25}H_{27}N_5O_2S$

Calculated: C, 65.05; H, 5.90; N, 15.17

Found: C, 64.81; H, 5.91; N, 14.90

Reference Example 56

4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl] benzamide

After dissolving 2.05 g of nickel chloride·6H$_2$O in 32 ml of methanol and adding 1.18 g of sodium borohydride at room temperature, an N,N-dimethylformamide solution containing 6.41 g of 4-[2-[(2-chloro-3-nitroquinolin-4-yl)amino]ethyl] benzamide was added. Next, 0.65 g of sodium borohydride was gradually added. After filtering off the insoluble portion, the solvent was distilled off under reduced pressure and a mixed solution of water, ethyl acetate and methanol was added to the obtained residue prior to extraction. After washing the organic layer with saturated saline and dewatering, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography [silica gel, methylene chloride/methanol (30:1-10:1)] to obtain 2.88 g of light brown crystals. Recrystallization from ethanol yielded light yellow crystals with a melting point of 220.0-220.5°C.

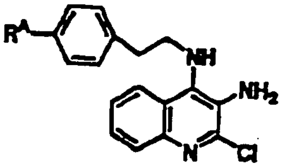
Elemental analysis: $C_{18}H_{17}ClN_4O$

Calculated: C, 63.44; H, 5.03; N, 16.44

Found: C, 63.28; H, 4.93; N, 16.24

The compounds for Reference Examples 57-94 listed in Tables 13 to 25 were obtained by the same method as Reference Example 56.

Table 13



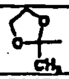
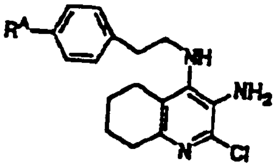
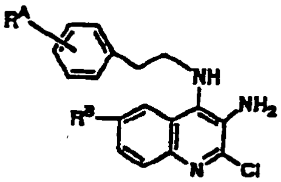
	R^A	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.57	CONHMe	light green crystals (EtOH) mp: 148.0-150.0°C	$C_{19}H_{19}ClN_4O$ Calc.: C,64.31; H,5.40; N,15.79 Found: C,64.39; H,5.41; N,15.97
Ref. Ex.58	OH	faint brown crystals (AcOEt) mp: 218.0-220.0°C	$C_{17}H_{16}ClN_3O$ Calc.: C,65.07; H,5.14; N,13.39 Found: C,65.04; H,4.93; N,13.29
Ref. Ex. 59	CO_2Et	faint brown needle-like crystals (iso-Pr_2O) mp: 113.0-115.0°C	$C_{20}H_{20}ClN_3O_2$ Calc.: C,64.95; H,5.45; N,11.36 Found: C,65.09; H,5.41; N,11.40
Ref. Ex. 60		light green crystals (EtOH) mp: 113.0-115.0°C	$C_{21}H_{22}ClN_3O_2$ Calc.: C,65.71; H,5.78; N,10.95 Found: C,65.61; H,5.82; N,10.95
Ref. Ex. 61	SO_2NH_2	brown needle-like crystals (MeOH) mp: 202.5-204.0°C	$C_{17}H_{17}ClN_4O_2S$ Calc.: C,54.18; H,4.55; N,14.87 Found: C,54.11; H,4.47; N,15.07
Ref. Ex. 62	NHMs	light brown crystals (AcOEt-n-Hexane) mp: 125.5-126.5°C	$C_{18}H_{19}ClN_4O_2S$ Calc.: C,55.31; H,4.90; N,14.33 Found: C,55.14; H,4.81; N,14.09
Ref. Ex. 63	NHTs	colorless crystals (iso-PrOH) mp: 142.0-142.5°C	$C_{24}H_{23}ClN_4O_2S$ Calc.: C,61.73; H,4.96; N,12.00 Found: C,61.61; H,4.84; N,11.82
Ref. Ex. 64	NHAc	light yellow prism crystals (CH_2Cl_2) mp: 161.5-163.5°C	$C_{19}H_{19}ClN_4O$ Calc.: C,64.31; H,5.40; N,15.79 Found: C,64.12; H,5.24; N,15.65

Table 14



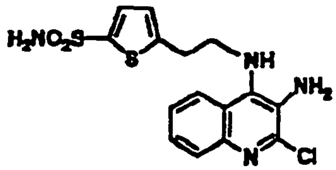
	R^A	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.65	SO_2NH_2	light brown crystals (DMF-H_2O) mp: 201.5-202.5°C	$C_{17}H_{21}ClN_4O_2S$ Calc.: C,53.61; H,5.56; N,14.71 Found: C,53.67; H,5.46; N,14.72
Ref. Ex.66	NHAc	colorless crystals (Benzene) mp: 134.0-134.5°C	$C_{19}H_{23}ClN_4O$ Calc.: C,63.59; H,6.46; N,15.61 Found: C,63.87; H,6.50; N,15.50
Ref. Ex.67	NMeAc	brown needle-like crystals (AcOEt) mp: 156.0-158.0°C	$C_{20}H_{25}ClN_4O$ Calc.: C,64.42; H,6.76; N,15.03 Found: C,64.38; H,6.75; N,14.93
Ref. Ex.68	CHMeNHAc	colorless crystals (CH_2Cl_2-n-Hexane) mp: 132.0-134.0°C	$C_{21}H_{27}ClN_4O$ Calc.: C,65.19; H,7.03; N,14.48 Found: C,65.08; H,7.15; N,14.40

Table 15



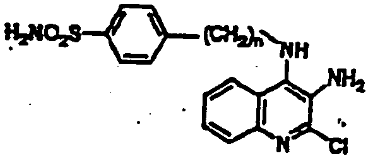
	R^A	R^B	Properties (recrystallization, solvent)	Elemental analysis
Ref. Ex.69	m-SO_2NH_2	H	greenish brown crystals (CH_3CN) mp: 158.0-160.0°C	$C_{17}H_{17}ClN_4O_2S\cdot 1/8H_2O$ Calc.: C,53.86; H,4.59; N,14.78 Found: C,53.78; H,4.34; N,14.67
Ref. Ex.70	p-SO_2NH_2	Me	light brown crystals (EtOH) mp: 201.0-202.0°C	$C_{18}H_{19}ClN_4O_2S$ Calc.: C,55.31; H,4.90; N,14.33 Found: C,55.32; H,4.96; N,14.11
Ref. Ex.71	p-SO_2NH_2	OMe	light brown crystals (EtOH) mp: 196.5-198.0°C	$C_{18}H_{19}ClN_4O_3S$ Calc.: C,53.13; H,4.71; N,13.77 Found: C,53.15; H,4.71; N,13.87

Table 16



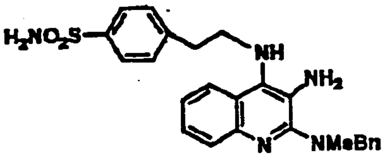
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.72	light brown crystals (AcOEt) mp: 176.0-177.0°C	$C_{15}H_{15}ClN_4O_2S_2$ Calc.: C,47.05; H,3.95; N,14.63 Found: C,47.03; H,3.89; N,14.41

Table 17



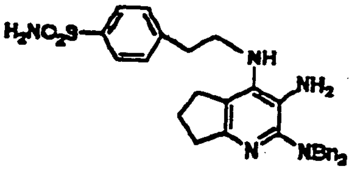
	n	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.73	1	light yellowish brown needle-like crystals (EtOH) mp: 202.0-203.0°C	$C_{16}H_{15}ClN_4O_2S$ Calc.: C,52.96; H,4.17; N,15.44 Found: C,52.88; H,4.29; N,15.19
Ref. Ex.74	3	light green needle-like crystals (MeOH) mp: 163.0-166.0°C	$C_{18}H_{19}ClN_4O_2S$ Calc.: C,55.31; H,4.90; N,14.33 Found: C,55.21; H,4.99; N,14.09

Table 18



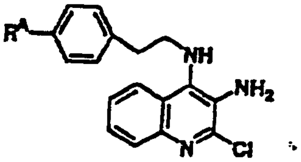
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.75	light yellow crystals (AcOEt) mp: 182.0-183.0°C	$C_{25}H_{27}N_5O_2S$ Calc.: C,65.05; H,5.90; N,15.17 Found: C,64.81; H,5.91; N,14.90

Table 19



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.76	gray crystals (DMF-H_2O) mp: 208.0-210.0°C	$C_{30}H_{33}N_5O_2S$ Calc.: C,68.28; H,6.30; N,13.27 Found: C,68.30; H,6.30; N,13.25

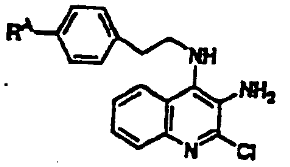
Table 20



	R^A	Properties
Ref. Ex.77	SO_2NHMe	green liquid NMR spectrum δ (DMSO-d_6) ppm: 2.38(3H, d, J=5.5Hz), 2.93(2H, t, J=7.5Hz), 3.50(2H, td, J=7.5, 7Hz), 4.93(2H, br-s), 5.27(1H, t, J=7Hz), 7.24(1H, q, J=5.5Hz), 7.35-7.45(4H, m), 7.65(2H, d, J=8.5Hz), 7.66(1H, dd, J=8.5,1Hz), 7.90(1H, dd, J=8.5, 1Hz), 7.95(1H, br-s) IR spectrum ν(liq) cm^{-1}: 3360, 1360, 1184 Mass spectrum m/z: 390, 392(3:1, M^+)
Ref. Ex.78	SO_2NHEt	green liquid NMR spectrum δ (DMSO-d_6) ppm: 0.95(3H, t, J=7.5Hz), 2.70-2.80(2H, m), 2.95(2H, t, J=7.5Hz), 3.50(2H, q, J=7.5Hz), 4.90(2H, br-s), 5.25(1H, t, J=7.5Hz), 7.30-7.45(5H, m), 7.60-7.80(3H, m), 7.80-7.90(1H, m) IR spectrum ν(liq) cm^{-1}: 3352, 1386, 1184 Mass spectrum m/z: 404, 406(3:1, M^+)
Ref. Ex.79	SO_2NH-n-Pr	green liquid NMR spectrum δ (DMSO-d_6) ppm: 0.80(3H, t, J=7Hz), 1.35(2H, sextet, J=7Hz), 2.65(2H, q, J=7Hz), 2.90(2H, t, J=7.5Hz), 3.50(2H, q, J=7.5Hz), 4.95(2H, br-s), 5.25(1H, t, J=7.5Hz), 7.35-7.45(5H, m), 7.65-7.70(3H, m), 7.85-7.95(1H, m) IR spectrum ν(liq) cm^{-1}: 3352, 1380, 1160
Ref. Ex.80	SO_2NMe_2	deep green liquid NMR spectrum δ (DMSO-d_6) ppm: 2.57(6H, s), 2.96(2H, t, J=7Hz), 3.53(2H, q, J=7Hz), 4.93(2H, br-s), 5.29(1H, t, J=7Hz), 7.35-7.45(2H, m), 7.44(2H, d, J=8.5Hz), 7.59(2H, d, J=8.5Hz), 7.66(1H, dd, J=8, 1Hz), 7.90(1H, dd, J=8, 1Hz) IR spectrum ν(liq) cm^{-1}: 3360, 1338, 1186 Mass spectrum m/z: 404, 406(3:1, M^+)
		dark green liquid NMR spectrum δ (DMSO-d_6) ppm: 2.83(2H, t,

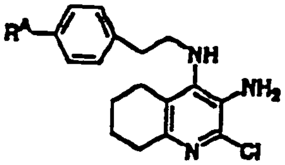
Ref. Ex.81	CH_2OH	J=7.5Hz), 3.45(2H, q, J=7.5Hz), 4.45(2H, d, J=5.5Hz), 4.90(2H, s), 4.96(1H, t, J=5.5Hz), 5.24(1H, t, J=7.5Hz), 7.16(2H, d, J=8Hz), 7.21(2H, d, J=8Hz), 7.35-7.45(2H, m), 7.68(1H, dd, J=8.5,2Hz), 7.97(1H, dd, J=8.5,2Hz)
	–	IR spectrum V(liq) cm^{-1}: 3352 Mass spectrum m/z: 327, 329(3:1, M^+)

Table 21



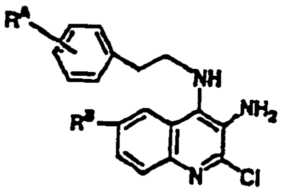
	R^A	Properties
Ref. Ex.82	NBn$_2$	brown liquid NMR spectrum δ (CDCl$_3$) ppm: 2.82(2H, t, J=6.5Hz), 3.44(2H, q, J=6.5Hz), 3.76(1H, t, J=6.5Hz), 3.85(2H, br-s), 4.67(4H, s), 6.73(2H, d, J=8.5Hz), 7.06(2H, d, J=8.5Hz), 7.20-7.40(1H, m), 7.40-7.50(2H, m), 7.86(1H, d, J=8Hz) IR spectrum ν(liq) cm^{-1}: 3440, 3356 Mass spectrum m/z: 492, 494(3:1, M$^+$)
Ref. Ex.83	CHMeNHAc	brown liquid NMR spectrum δ (DMSO-d$_6$) ppm: 1.30(3H, d, J=7.5Hz), 1.82(3H, s), 2.81(2H, t, J=7.5Hz), 3.44(2H, td, J=7.5, 7Hz), 4.85(1H, q, J=7.5Hz), 4.90(2H, s), 5.24(1H, t, J=7Hz), 7.13(2H, d, J=8Hz), 7.18(2H, d, J=8Hz), 7.35-7.50(2H, m), 7.67(1H, dd, J=8,1Hz), 7.90-8.00(1H, m), 8.07(1H, d, J=7.5Hz) IR spectrum ν(liq) cm^{-1}: 3336, 1656 Mass spectrum m/z: 382(M$^+$)
Ref. Ex.84	NMeAc	colorless liquid NMR spectrum δ (DMSO-d$_6$) ppm: 1.74(3H, s), 2.87(2H, t, J=7Hz), 3.11(3H, s), 3.50(2H, q, J=7Hz), 4.90(2H, br-s), 5.26(1H, t, J=7Hz), 7.15(2H, d, J=8.5Hz), 7.24(2H, d, J=8.5Hz), 7.30-7.45(2H, m), 7.67(1H, dd, J=8.5,1Hz), 7.92(1H, dd, J=8.5, 1Hz) IR spectrum ν(liq) cm^{-1}: 3344, 1646 Mass spectrum m/z: 368(M$^+$)

Table 22



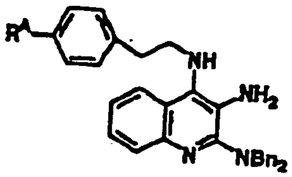
	R^A	Properties
Ref. Ex.85	CH_2OH	brown liquid NMR spectrum δ (DMSO-d_6) ppm: 1.60-1.75(4H, m), 2.44(2H, t, J=6Hz), 2.58(2H, t, J=6Hz), 2.72(2H, t, J=7.5Hz), 3.28(2H, td, J=7.5, 6Hz), 4.36(2H, br-s), 4.41(1H, t, J=6Hz), 4.45(2H, d, J=6Hz), 4.96(1H, t, J=6Hz), 7.13(2H, d, J=8.5Hz), 7.21(2H, d, J=8.5Hz) IR spectrum V(liq) cm^{-1}: 3352 Mass spectrum m/z: 331, 333(3:1, M^+)
Ref. Ex.86	NHMs	light brown liquid NMR spectrum δ (DMSO-d_6) ppm: 1.60-1.75(4H, m), 2.41(2H, t, J=6Hz), 2.57(2H, t, J=6Hz), 2.70(2H, t, J=7Hz), 2.92(3H, s), 3.28(2H, q, J=7Hz), 4.36(2H, br-s), 4.40(1H, t, J=7Hz), 7.11(2H, d, J=8.5Hz), 7.14(2H, d, J=8.5Hz), 9.46(1H, br-s) IR spectrum V(liq) cm^{-1}: 3356, 3264, 1336, 1154 Mass spectrum m/z: 394, 396(3:1, M^+)
Ref. Ex.87	NMeBn	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.60-1.80(4H, m), 2.20-2.35(2H, m), 2.65-2.80(4H, m), 3.02(3H, s), 3.20-3.40(3H, m), 3.52(2H, br-s), 4.52(2H, s), 6.70(2H, d, J=8.5Hz), 7.05(2H, d, J=8.5Hz), 7.15-7.40(5H, m), 7.21(2H, d, J=7.5Hz), 7.20-7.30(1H, m), 7.31(2H, t, J=7.5Hz) IR spectrum V(liq) cm^{-1}: 3356 Mass spectrum m/z: 420, 422(3:1, M^+)

Table 23



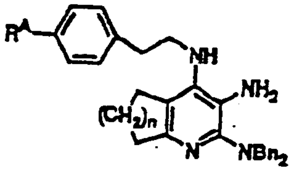
	R^A	R^B	Properties
Ref. Ex.88	o-SO_2NH_2	H	light green liquid NMR spectrum δ (DMSO-d_6) ppm: 3.32(2H, t, J=8Hz), 3.52(2H, td, J=8, 7Hz), 4.94(2H, br-s), 5.22(1H, t, J=7Hz), 7.35-7.45(7H, m), 7.49(1H, td, J=6,1Hz), 7.67(1H, dd, J=8,1Hz), 7.88(1H, dd, J=8,1HZ), 7.95-8.00(1H, m) IR spectrum V(liq) cm^{-1}: 3428, 3330, 1180 Mass spectrum m/z: 376, 378(3:1, M^+)
Ref. Ex.89	p-SO_2NH_2	Cl	reddish brown crystals NMR spectrum δ (DMSO-d_6) ppm: 2.91(2H, t, J=7.5Hz), 3.43(2H, td, J=7.5,6.5Hz), 5.08(2H, br-s), 5.35(1H, t, J=6.5Hz), 7.16(2H, br-s), 7.39(1H, dd, J=9, 2.5Hz), 7.40(2H, d, J=8.5Hz), 7.69(1H, d, J=9Hz), 7.73(2H, d, J=8.5Hz), 8.01(1H, d, J=2.5Hz) IR spectrum V(liq) cm^{-1}: 3444, 3372, 1330, 1160 Mass spectrum m/z: 410, 412, 414(9:6:1, M^+)

Table 24



	R^1	Properties
Ref. Ex.90	CHMeOH	yellowish brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.50(3H, d, J=6Hz), 1.75(1H, br-s), 2.92(2H, t, J=7Hz), 3.46(2H, t, J=7Hz), 3.50(1H, br-s), 4.00(2H, br-s), 4.50(4H, s), 4.90(1H, q, J=6Hz), 7.15-7.40(17H, m), 7.77(1H, d, J=7.5Hz) IR spectrum V(liq) cm^{-1}: 3416 Mass spectrum m/z: 502(M^+)
Ref. Ex.91	NMeAc	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.86(3H, br-s), 2.94(2H, t, J=7Hz), 3.25(3H, br-s), 3.48(2H, td, J=7,5.5Hz), 3.60(1H, t, J=5.5Hz), 4.01(2H, br-s), 4.51(4H, s), 7.12(2H, d, J=8Hz), 7.18-7.42(15H, m), 7.79(1H, d, J=8.5Hz) IR spectrum V(liq) cm^{-1}: 3420, 3370, 1660 Mass spectrum m/z: 529(M^+)
Ref. Ex.92	NHAc	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 2.17(3H, s), 2.88(2H, t, J=6.5Hz), 3.44(2H, t, J=6.5Hz), 3.57(1H, br-s), 4.00(2H, br-s), 4.50(4H, s), 7.15(1H, br-s), 7.15-7.30(13H, m), 7.36(1H, t, J=7.5Hz), 7.40-7.45(3H, m), 7.78(1H, d, J=8.5Hz) IR spectrum V(liq) cm^{-1}: 3324, 1670 Mass spectrum m/z: 515(M^+)

Table 25



	R^A	n	Properties
Ref. Ex.93	NHAc	2	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.60-1.80(4H, m), 2.17(3H, s), 2.20-2.35(2H, m), 2.65-2.75(2H, m), 2.73(2H, t, J=6.5Hz), 3.34(2H, t, J=6.5Hz), 3.61(2H, br-s), 4.23(4H, s), 7.11(2H, d, J=8Hz), 7.15-7.33(10H, m), 7.41(2H, d, J=8Hz) IR spectrum ν(liq) cm^{-1}: 3412, 3320, 1668 Mass spectrum m/z: 519(M^+)
Ref. Ex.94	NBn_2	1	green liquid NMR spectrum δ ($CDCl_3$) ppm: 2.02(2H, quintet, J=6.5Hz), 2.62(2H, t, J=6.5Hz), 2.83(2H, t, J=6.5Hz), 2.87(2H, t, J=6.5Hz), 3.17(2H, br-s), 3.49(2H, t, J=6.5Hz), 3.65(1H, br-s), 4.12(4H, s), 4.63(4H, s), 6.63(2H, d, J=8.5Hz), 6.85(2H, d, J=8.5Hz), 7.15(2H, t, J=7.5Hz), 7.20-7.30(14H, m), 7.32(4H, t, J=7.5Hz) IR spectrum ν(liq) cm^{-1}: 3384 Mass spectrum m/z: 643(M^+)

Reference Example 95

4-[2-(4-chloro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzamide

Upon adding 10 ml of ethyl orthoformate to 2.45 g of 4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl]benzamide, the mixture was stirred at 80-120°C for 5 hours. After addition of n-hexane at room temperature, the precipitated crystals were filtered off and washed with isopropyl ether to obtain 2.29 g of light brown crystals. Recrystallization from acetonitrile yielded colorless crystals with a melting point of 287.0-288.0°C.

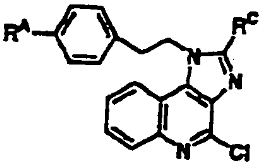
Elemental analysis: $C_{19}H_{15}ClN_4O$

Calculated: C, 65.05; H, 4.31; N, 15.97

Found: C, 64.80; H, 4.08; N, 16.15

The compounds for Reference Examples 96-147 listed in Tables 26 to 34 were obtained by the same method as Reference Example 95.

Table 26



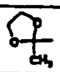
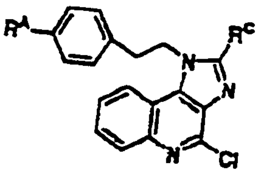
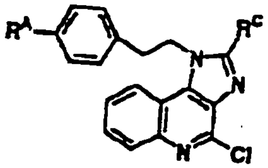
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.96	CONHMe	H	light brown crystals (EtOH) mp: 220.0-222.0°C	$C_{20}H_{17}ClN_4O$ Calc.: C,65.84; H,4.70; N,15.36 Found: C,65.66; H,4.76; N,15.07
Ref. Ex.97	OH	H	light brown crystals (DMF-H_2O) mp: 231.0-232.0°C	$C_{18}H_{14}ClN_3O$ Calc.: C,66.77; H,4.36; N,12.98 Found: C,67.04; H,4.06; N,13.07
Ref. Ex.98	CO_2Et	H	light brown crystals (iso-PrOH) mp: 128.0-129.0°C	$C_{21}H_{18}ClN_3O_2$ Calc.: C,66.40; H,4.78; N,11.06 Found: C,66.50; H,4.57; N,11.05
Ref. Ex.99		H	colorless crystals (EtOH) mp: 165.5-167.5°C	$C_{22}H_{20}ClN_3O_2$ Calc.: C,67.09; H,5.12; N,10.67 Found: C,67.13; H,5.08; N,10.72
Ref. Ex.100	SO_2NHEt	H	light green crystals (EtOH) mp: 205.0-206.5°C	$C_{20}H_{19}ClN_4O_2S$ Calc.: C,57.90; H,4.62; N,13.50 Found: C,58.18; H,4.59; N,13.53
Ref. Ex.101	SO_2NH-n-Pr	H	light yellow plate crystals (MeOH) mp: 231.5-234.5°C	$C_{21}H_{21}ClN_4O_2S$ Calc.: C,58.80; H,4.93; N,13.06 Found: C,58.68; H,4.71; N,12.92
Ref. Ex.102	SO_2NMe_2	H	light yellow crystals (CH_3CN) mp: 233.5-235.0°C	$C_{20}H_{19}ClN_4O_2S$ Calc.: C,57.90; H,4.62; N,13.50 Found: C,57.71; H,4.53; N,13.26
Ref. Ex.103	SO_2NH_2	H	light yellowish brown crystals (DMF-H_2O) mp: 265.0-266.5°C	$C_{18}H_{15}ClN_4O_2S$ Calc.: C,55.89; H,3.91; N,14.48 Found: C,55.72; H,3.73; N,14.52
Ref. Ex.104	SO_2NHMe	H	yellow crystals (DMF-H_2O) mp: 216.5-217.5°C	$C_{19}H_{17}ClN_4O_2S$ Calc.: C,56.93; H,4.27; N,13.98 Found: C,56.79; H,4.43; N,13.80

Table 27



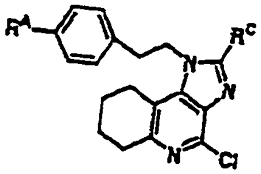
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.105	SO_2NHMe	Me	colorless crystals (DMF-H_2O) mp: 253.0-254.0°C	$C_{20}H_{19}ClN_4O_2S$ Calc.: C,57.90; H,4.62; N,13.50 Found: C,57.92; H,4.40; N,13.48
Ref. Ex.106	SO_2NHMe	Et	light yellow crystals (DMF-H_2O) mp: 272.5-273.5°C	$C_{21}H_{21}ClN_4O_2S$ Calc.: C,58.80; H,4.93; N,13.06 Found: C,58.61; H,4.87; N,12.95
Ref. Ex.107	SO_2NHMe	n-Pr	light yellow crystals (DMF-H_2O) mp: 260.5-261.5°C	$C_{22}H_{23}ClN_4O_2S$ Calc.: C,59.65; H,5.23; N,12.65 Found: C,59.70; H,5.21; N,12.51
Ref. Ex.108	SO_2NHMe	n-Bu	light brown crystals (DMF-H_2O) mp: 205.5-206.0°C	$C_{23}H_{25}ClN_4O_2S$ Calc.: C,60.45; H,5.51; N,12.26 Found: C,60.45; H,5.47; N,12.25
Ref. Ex.109	CH_2OH	H	light brown crystals (EtOH) mp: 191.0-193.0°C	$C_{19}H_{16}ClN_3O$ Calc.: C,67.56; H,4.77; N,12.44 Found: C,67.58; H,4.58; N,12.27
Ref. Ex.110	CH_2OH	n-Bu	light yellow crystals (AcOEt) mp: 177.5-178.5°C	$C_{23}H_{24}ClN_3O$ Calc.: C,70.13; H,6.14; N,10.67 Found: C,70.16; H,6.03; N,10.61
Ref. Ex.111	NHMs	H	colorless prism crystals (EtOH) mp: 218.5-220.0°C	$C_{19}H_{17}ClN_4O_2S$ Calc.: C,56.93; H,4.27; N,13.98 Found: C,56.95; H,4.26; N,13.77
Ref. Ex.112	NHMs	Me	light brown crystals (EtOH) mp: 249.0-250.0°C	$C_{20}H_{19}ClN_4O_2S$ Calc.: C,57.90; H,4.62; N,13.50 Found: C,57.96; H,4.74; N,13.21
Ref. Ex.113	NHMs	Et	light brown prism crystals (EtOH) mp: 240.0-240.5°C	$C_{21}H_{21}ClN_4O_2S$ Calc.: C,58.80; H,4.93; N,13.06 Found: C,58.67; H,4.84; N,12.94
Ref. Ex.114	NHMs	n-Pr	colorless crystals (MeOH) mp: 221.5-224.0°C	$C_{22}H_{23}ClN_4O_2S$ Calc.: C,59.65; H,5.23; N,12.65 Found: C,59.65; H,5.15; N,12.63
Ref. Ex.115	NHMs	n-Bu	light yellow crystals (MeOH) mp: 199.5-200.5°C	$C_{23}H_{25}ClN_4O_2S$ Calc.: C,60.45; H,5.51; N,12.26 Found: C,60.45; H,5.44; N,12.20

Table 28



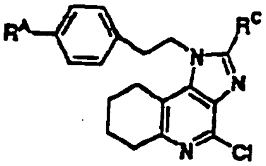
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.116	NHTs	H	light yellow needle-like crystals (DMF-H_2O) mp: 246.5-247.0°C	$C_{25}H_{21}ClN_4O_2S$ Calc.: C,62.95; H,4.44; N,11.75 Found: C,62.79; H,4.36; N,12.03
Ref. Ex.117	NHAc	H	colorless crystals (EtOH) mp: 276.0-277.0°C	$C_{20}H_{17}ClN_4O$ Calc.: C,65.84; H,4.70; N,15.36 Found: C,65.66; H,4.76; N,15.09
Ref. Ex.118	NHAc	Me	faint yellow needle-like crystals (MeOH) mp: 250.0-251.0°C	$C_{21}H_{19}ClN_4O$ Calc.: C,66.58; H,5.05; N,14.79 Found: C,66.46; H,5.03; N,14.80
Ref. Ex.119	NHAc	Et	yellowish orange crystals (AcOEt) mp: 215.0-215.5°C	$C_{22}H_{21}ClN_4O$ Calc.: C,67.26; H,5.39; N,14.26 Found: C,67.44; H,5.41; N,14.22
Ref. Ex.120	NHAc	n-Bu	light brown crystals (MeOH) mp: 220.0-220.5°C	$C_{24}H_{25}ClN_4O$ Calc.: C,68.48; H,5.99; N,13.31 Found: C,68.47; H,6.00; N,13.58
Ref. Ex.121	NMeAc	H	colorless needle-like crystals (EtOH) mp: 137.0-137.5°C	$C_{21}H_{19}ClN_4O$ Calc.: C,66.58; H,5.05; N,14.79 Found: C,66.50; H,4.96; N,14.77
Ref. Ex.122	NMeAc	Me	colorless crystals (iso-PrOH) mp: 248.5-249.0°C	$C_{22}H_{21}ClN_4O$ Calc.: C,67.26; H,5.39; N,14.26 Found: C,67.30; H,5.42; N,14.24
Ref. Ex.123	NMeAc	Et	faint brown prism crystals (THF) mp: 233.0-234.5°C	$C_{23}H_{23}ClN_4O$ Calc.: C,67.89; H,5.70; N,13.77 Found: C,68.06; H,5.58; N,13.94
Ref. Ex.124	NMeAc	n-Bu	colorless crystals (AcOEt-iso-Pr_2O) mp: 175.5-176.0°C	$C_{25}H_{27}ClN_4O$ Calc.: C,69.03; H,6.26; N,12.88 Found: C,69.07; H,6.22; N,12.85
Ref. Ex.125	NBn_2	n-Bu	colorless crystals (AcOEt) mp: 151.5-152.5°C	$C_{36}H_{35}ClN_4$ Calc.: C,77.33; H,6.31; N,10.02 Found: C,77.42; H,6.29; N,10.11
Ref. Ex.126	CHMeNHAc	Et	light yellow crystals (AcOEt) mp: 188.5-190.5°C	$C_{24}H_{25}ClN_4O$ Calc.: C,68.48; H,5.99; N,13.31 Found: C,68.27; H,6.11; N,13.21

Table 29



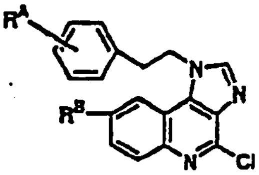
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.127	SO_2NH_2	H	light yellowish brown crystals ($DMF-H_2O$) mp: 247.5-249.5°C	$C_{18}H_{19}ClN_4O_2S$ Calc.: C,55.31; H,4.90; N,14.33 Found: C,55.03; H,4.76; N,14.40
Ref. Ex.128	NHMs	H	colorless crystals (iso-PrOH) mp: 202.0-204.0°C	$C_{19}H_{21}ClN_4O_2S$ Calc.: C,56.36; H,5.23; N,13.84 Found: C,56.51; H,5.41; N,13.57
Ref. Ex.129	NHMs	Me	colorless prism crystals (EtOH) mp: 247.0-248.0°C	$C_{20}H_{23}ClN_4O_2S$ Calc.: C,57.34; H,5.53; N,13.37 Found: C,57.34; H,5.72; N,13.16
Ref. Ex.130	NHMs	n-Bu	colorless needle-like crystals (AcOEt) mp: 164.0-165.0°C	$C_{23}H_{29}ClN_4O_2S$ Calc.: C,59.92; H,6.34; N,12.15 Found: C,59.70; H,6.22; N,11.95
Ref. Ex.131	NHAc	H	colorless crystals (MeOH) mp: 247.0-249.0°C	$C_{20}H_{21}ClN_4O$ Calc.: C,64.95; H,6.00; N,15.15 Found: C,65.14; H,5.72; N,15.23
Ref. Ex.132	NHAc	Me	colorless needle-like crystals (EtOH) mp: 249.0-250.0°C	$C_{21}H_{23}ClN_4O$ Calc.: C,65.87; H,6.05; N,14.63 Found: C,65.82; H,6.05; N,14.61
Ref. Ex.133	NHAc	Et	colorless crystals (AcOEt) mp: 202.0-202.5°C	$C_{22}H_{25}ClN_4O$ Calc.: C,66.57; H,6.35; N,14.12 Found: C,66.32; H,6.24; N,14.04
Ref. Ex.134	NHAc	n-Bu	colorless crystals (AcOEt) mp: 192.0-193.0°C	$C_{24}H_{29}ClN_4O$ Calc.: C,67.83; H,6.88; N,13.18 Found: C,67.89; H,7.02; N,12.93
Ref. Ex.135	NMeAc	H	light brown crystals (iso-PrOH) mp: 191.5-192.5°C	$C_{21}H_{23}ClN_4O$ Calc.: C,65.87; H,6.05; N,14.63 Found: C,66.07; H,6.02; N,14.61
Ref. Ex.136	NMeAc	Me	colorless crystals (EtOH) mp: 229.0-230.0°C	$C_{22}H_{25}ClN_4O$ Calc.: C,66.57; H,6.35; N,14.12 Found: C,66.40; H,6.35; N,14.11
Ref. Ex.137	NMeAc	Et	colorless needle-like crystals (THF) mp: 217.5-218.5°C	$C_{23}H_{27}ClN_4O$ Calc.: C,67.22; H,6.62; N,13.63 Found: C,67.17; H,6.62; N,13.68
Ref. Ex.138	NMeAc	n-Bu	colorless crystals ($AcOEt-iso-Pr_2O$) mp: 147.0-148.0°C	$C_{25}H_{31}ClN_4O$ Calc.: C,68.40; H,7.12; N,12.76 Found: C,68.52; H,7.17; N,12.77

Table 30



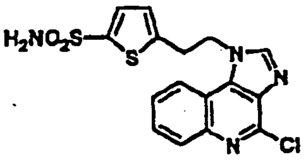
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.139	CHMeNHAc	H	colorless crystals (AcOEt) mp: 192.5-193.5°C	$C_{22}H_{25}ClN_4O$ Calc.: C,66.57; H,6.35; N,14.12 Found: C,66.63; H,6.47; N,14.29

Table 31



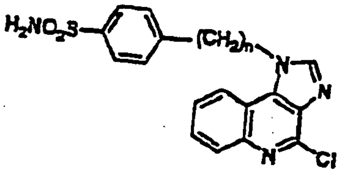
	R^A	R^B	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.140	m-SO_2NH_2	H	brown crystals (DMF-H_2O) mp: 261.0-262.5°C	$C_{18}H_{15}ClN_4O_2S \cdot 1/4H_2O$ Calc.: C,55.24; H,3.99; N,14.32 Found: C,55.06; H,3.71; N,14.44
Ref. Ex.141	p-SO_2NH_2	Me	light brown crystals (CH_3CN) mp: 276.5-278.0°C	$C_{19}H_{17}ClN_4O_2S$ Calc.: C,56.93; H,4.27; N,13.98 Found: C,56.66; H,4.11; N,13.81
Ref. Ex.142	p-SO_2NH_2	OMe	light brown crystals (CH_3CN) mp: 266.5-268.0°C	$C_{19}H_{17}ClN_4O_3S$ Calc.: C,54.74; H,4.11; N,13.44 Found: C,54.47; H,3.96; N,13.29
Ref. Ex.143	p-SO_2NH_2	Cl	light brown crystals (CH_3CN) mp: 263.0-264.0°C	$C_{18}H_{14}Cl_2N_4O_2S$ Calc.: C,51.32; H,3.35; N,13.30 Found: C,51.13; H,3.16; N,13.07

Table 32



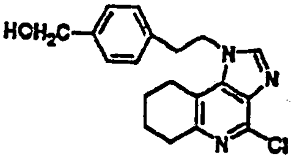
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.144	light brown crystals (CH_3CN) mp: 238.5-239.5°C	$C_{16}H_{13}ClN_4O_2S_2$ Calc.: C,48.91; H,3.34; N,14.26 Found: C,49.08; H,3.23; N,14.53

Table 33



	n	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.145	1	colorless needle-like crystals (EtOH) mp: 260.0-261.0°C	$C_{17}H_{13}ClN_4O_2S$ Calc.: C,54.77; H,3.51; N,15.03 Found: C,54.73; H,3.48; N,14.84
Ref. Ex.146	3	colorless crystals (DMF-H_2O) mp: 183.5-184.0°C	$C_{19}H_{17}ClN_4O_2S$ Calc.: C,56.93; H,4.27; N,13.98 Found: C,56.65; H,4.25; N,13.68

Table 34



	Properties
Ref. Ex.147	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 1.81(4H, br-s), 2.88(2H, br-s), 3.10(2H, br-s), 3.10(2H, t, J=7.5Hz), 4.50(2H, s), 4.61(2H, t, J=7.5Hz), 5.24(1H, s), 7.10(2H, d, J=8Hz), 7.22(2H, d, J=8Hz), 8.04(1H, s) IR spectrum ν(liq) cm^{-1}: 3436

Reference Example 148

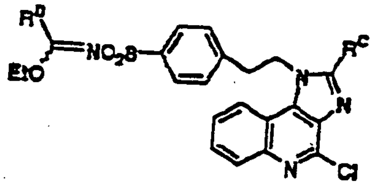
4-[2-(4-chloro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]-N-(1-ethoxyethylidene)benzenesulfonamide

Upon adding 9.4 ml of ethyl orthoformate to 2.34 g of 4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl] benzenesulfonamide, the mixture was stirred at 140°C overnight. After cooling the reaction solution, n-hexane was added for decantation, and then the residue was purified by column chromatography [silica gel, ethyl acetate/n-hexane (1:1-4:1)]. This was crystallized from a mixed solution of ethyl acetate and n-hexane to obtain 1.67 g of crystals. Recrystallization from ethyl acetate yielded yellow

needle-like crystals with a melting point of 151.0-152.0°C.
Elemental analysis: $C_{23}H_{23}ClN_4O_3S$
Calculated: C, 58.65; H, 4.92; N, 11.90
Found: C, 58.59; H, 4.70; N, 11.71

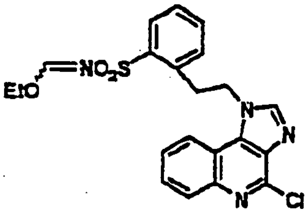
The compounds for Reference Examples 149-152 listed in Tables 35 and 36 were obtained by the same method as Reference Example 148.

Table 35



	R^C	R^D	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.149	Et	Et	light yellowish brown crystals (DMF) mp: 177.0-178.0°C	$C_{25}H_{27}ClN_4O_2S$ Calc.: C,60.17; H,5.45; N,11.23 Found: C,60.02; H,5.46; N,11.11
Ref. Ex.150	n-Pr	n-Pr	yellow needle-like crystals (iso-PrOH) mp: 117.0-117.5°C	$C_{27}H_{31}ClN_4O_2S$ Calc.: C,61.53; H,5.93; N,10.63 Found: C,61.41; H,5.90; N,10.84
Ref. Ex.151	n-Bu	n-Bu	yellowish brown crystals (AcOEt-n-Hex) mp: 99.0-100.5°C	$C_{29}H_{35}ClN_4O_2S$ Calc.: C,62.74; H,6.35; N,10.09 Found: C,62.58; H,6.41; N,10.13

Table 36



	Properties
Ref. Ex.152	reddish brown crystals NMR spectrum δ (DMSO-d_6) ppm: 1.00-1.25(3H, m), 3.71(2H, t, J=7Hz), 4.22(2H, q, J=7Hz), 5.09(2H, t, J=7Hz), 7.10-7.15(1H, m), 7.40-7.60(2H, m), 7.65-7.80(2H, m), 7.90-8.00(1H, m), 8.08(1H, dd, J=8, 1Hz), 8.25(1H, s), 8.50-8.55(1H, m), 8.65(1H, s) IR spectrum ν(liq) cm^{-1}: 1366, 1162 Mass spectrum m/z: 442, 444(3:1, M^+)

Reference Example 153

4-[2-(4-chloro-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl propionate

After dissolving 3.00 g of 4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl]benzyl alcohol in 75 ml of toluene, 3.1 ml of propionyl chloride was added. After stirring at room temperature for 3 hours, 0.17 g of p-toluenesulfonic acid·$1H_2O$ was added and reflux was carried out for 6 hours, after which the reaction mixture was concentrated under reduced pressure, the residue was dissolved in methylene chloride, and the mixture was washed first with 10% ammonia water, water and then saturated saline. After dewatering the methylene chloride layer, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography [silica gel, methylene chloride/methanol (50:1)] to obtain 1.70 g of light brown crystals. Recrystallization from isopropyl alcohol yielded light brown crystals with a melting point of 144.0-145.5°C.

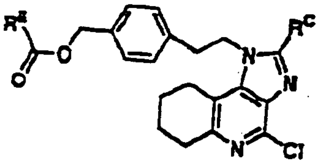
Elemental analysis: $C_{24}H_{24}ClN_3O_2$

Calculated: C, 68.32; H, 5.73; N, 9.96

Found: C, 68.32; H, 5.74; N, 9.98

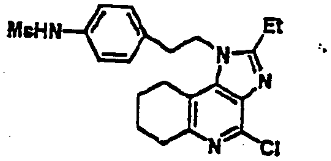
The compounds for Reference Examples 154-156 listed in Tables 37 and 38 were obtained by the same method as Reference Example 153.

Table 37



	R^C	R^E	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.154	Me	Me	colorless crystals (iso-PrOH) mp: 150.5-152.5°C	$C_{22}H_{24}ClN_3O_2$ Calc.: C,66.41; H,6.08; N,10.56 Found: C,66.30; H,6.25; N,10.63
Ref. Ex.155	Et	Et	colorless crystals (iso-PrOH-iso-Pr_2O) mp: 128.0-129.0°C	$C_{24}H_{28}ClN_3O_2$ Calc.: C,67.67; H,6.63; N,9.87 Found: C,67.57; H,6.52; N,9.91

Table 38



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.156	light brown crystals (iso-PrOH) mp: 187.0-189.0°C	$C_{21}H_{25}ClN_4O_2S$ Calc.: C,58.25; H,5.82; N,12.94 Found: C,58.31; H,5.98; N,12.90

Reference Example 157

4-[2-(2-ethoxymethyl-4-hydroxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide

Upon adding 23.7 ml of ethoxyacetic acid to 5.92 g of 4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl]benzenesulfonamide, the mixture was stirred at 80-130°C for 6 hours. After the reaction, the precipitated crystals were filtered off and washed with methylene chloride to obtain 3.90 g of crystals. Recrystallization from a mixed solution of N,N-dimethylformamide and water yielded colorless crystals with a melting point of 300°C or higher.

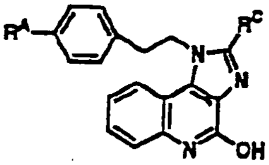
Elemental analysis: $C_{21}H_{22}N_4O_4 \cdot 1/2H_2O$

Calculated: C, 58.52; H, 5.26; N, 13.00

Found: C, 58.41; H, 5.00; N, 12.75

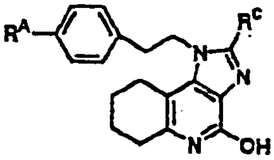
The compounds for Reference Examples 158-178 listed in Tables 39 to 46 were obtained by the same method as Reference Example 157.

Table 39



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.158	SO_2NH_2	iso-Pen	light brown crystals (DMF-H_2O) mp: ≥300°C	$C_{23}H_{26}N_4O_3S\cdot1/6H_2O$ Calc.: C,62.56; H,6.01; N,12.69 Found: C,62.27; H,5.80; N,12.57
Ref. Ex.159	SO_2NH_2	CF_3	light brown crystals (DMF-H_2O) mp: ≥300°C	$C_{19}H_{15}F_3N_4O_3S$ Calc.: C,52.29; H,3.46; N,12.84 Found: C,52.16; H,3.38; N,12.86
Ref. Ex.160	SO_2NH_2	$CH_2CH_2CF_3$	light brown crystals (DMF-H_2O) mp: 290.0-291.5°C, decomposition	$C_{21}H_{19}F_3N_4O_3S$ Calc.: C,54.31; H,4.12; N,12.06 Found: C,54.33; H,3.87; N,12.01
Ref. Ex.161	SO_2NH_2	CH_2OH	faint brown crystals (DMF-H_2O) mp: 294.0-296.0°C	$C_{19}H_{18}N_4O_4S$ Calc.: C,57.28; H,4.55; N,14.06 Found: C,57.17; H,4.60; N,14.06
Ref. Ex.162	SO_2NH_2	CH_2OMe	light brown crystals (EtOH) mp: 277.5-278.5°C	$C_{20}H_{20}N_4O_4S\cdot1/4H_2O$ Calc.: C,57.61; H,4.96; N,13.44 Found: C,57.52; H,5.04; N,13.34
Ref. Ex.163	NHMs	CH_2OEt	light brown crystals (MeOH) mp: 231.0-233.0°C	$C_{22}H_{24}N_4O_4S$ Calc.: C,59.98; H,5.49; N,12.72 Found: C,60.00; H,5.52; N,12.68
Ref. Ex.164	SO_2NHMe		light brown crystals (DMF-H_2O) mp: 288.0-289.0°C	$C_{23}H_{24}N_4O_3S$ Calc.: C,63.28; H,5.54; N,12.83 Found: C,63.07; H,5.41; N,12.57
Ref. Ex.165	SO_2NHMe	CH_2OEt	light yellow crystals (DMF-H_2O) mp: 268.5-270.0°C	$C_{22}H_{24}N_4O_4S$ Calc.: C,59.98; H,5.49; N,12.72 Found: C,60.09; H,5.44; N,12.90

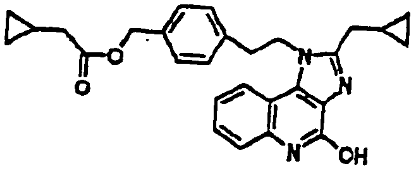
Table 40



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.166	SO_2NH_2	CH_2OEt	light brown crystals (DMF-H_2O) mp: ≥300°C	$C_{21}H_{26}N_4O_4S\cdot1/3H_2O$ Calc.: C,57.78; H,6.16; N,12.83 Found: C,57.54; H,6.16; N,12.68

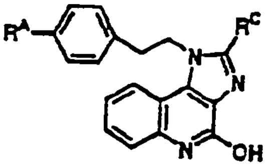
'Ref. Ex.167	NMeBn	CH_2OEt	colorless crystals (THF) mp: 235.0-238.5°C	$C_{29}H_{34}N_4O_2\cdot1/4H_2O$ Calc.: C,73.31; H,7.32; N,11.79 Found: C,73.43; H,7.25; N,11.92

Table 41



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.168	colorless needle-like crystals (AcOEt) mp: 186.0-186.5°C	$C_{28}H_{29}N_3O_3$ Calc.: C,73.82; H,6.42; N,9.22 Found: C,73.64; H,6.39; N,9.16

Table 42



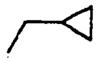
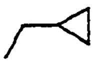
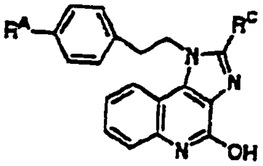
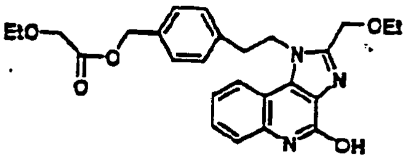
	R^A	R^C	Properties
Ref. Ex.169	SO_2NH_2	n-Pen	light brown crystals NMR spectrum δ (DMSO-d_6) ppm: 0.87(3H, t, J=7Hz), 1.15-1.40(4H, m), 1.63(2H, quintet, J=7Hz), 2.43(2H, t, J=7Hz), 3.20(2H, t, J=7Hz), 4.73(2H, t, J=7Hz), 7.21(2H, br-s), 7.29(2H, d, J=8Hz), 7.45(2H, t, J=8Hz), 7.50(1H, d, J=8Hz), 7.73(2H, d, J=8Hz), 8.07(1H, d, J=8Hz), 11.43(1H, br-s) IR spectrum V(KBr) cm^{-1}: 1660, 1336, 1162
Ref. Ex.170	SO_2NH_2	iso-Bu	yellowish brown crystals NMR spectrum δ (DMSO-d_6) ppm: 0.89(6H, d, J=7Hz), 2.05-2.15(1H, m), 2.32(2H, d, J=7Hz), 3.18(2H, t, J=7Hz), 4.74(2H, t, J=7Hz), 7.23(2H, br-s), 7.29(2H, d, J=8.5Hz), 7.30-7.35(1H, m), 7.40-7.51(2H, m), 7.73(2H, d, J=8.5Hz), 8.05-8.10(1H, m), 11.4(1H, br-s) IR spectrum V(KBr) cm^{-1}: 1652, 1348, 1162
Ref. Ex.171	SO_2NH_2		light yellow crystals NMR spectrum δ (DMSO-d_6) ppm: 0.15-0.25(2H, m), 0.45-0.55(2H, m), 1.05-1.10(1H, m), 2.55-2.60(2H, m), 3.22(2H, t, J=7Hz), 4.82(2H, t, J=7Hz), 7.24(2H, br-s), 7.34(2H, d, J=8Hz), 7.35-7.40(1H, m), 7.50-7.60(2H, m), 7.74(2H, d, J=8Hz), 8.10-8.15(1H, m), 11.72(1H, br-s) IR spectrum V(KBr) cm^{-1}: 1656, 1346, 1164
Ref. Ex.172	NHMs		colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 0.05-0.15(2H, m), 0.45-0.55(2H, m), 1.05-1.15(1H, m), 2.39(2H, d, J=7Hz), 2.91(3H, s), 3.07(2H, t, J=7Hz), 4.67(2H, t, J=7Hz), 7.02(2H, d, J=8.5Hz), 7.11(2H, d, J=8.5Hz), 7.28(1H, t, J=7.5Hz), 7.44(1H, t, J=7.5Hz), 7.49(1H, d, J=7.5Hz), 8.05(1H, d, J=7.5Hz), 9.54(1H, br-s), 11.41(1H, br-s) IR spectrum V(KBr) cm^{-1}: 1620, 1332, 1154

Table 43



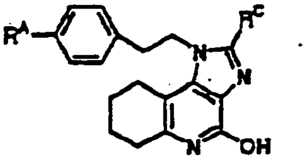
	R^A	R^C	Properties
Ref. Ex.173	SO_2NHMe	CH_2OH	light brown crystals NMR spectrum δ (DMSO-d_6) ppm: 2.38(3H, s), 3.27(2H, t, J=7.5Hz), 4.42(2H, s), 4.87(2H, t, J=7.5Hz), 5.56(1H, br-s), 7.25-7.35(2H, m), 7.40(2H, d, J=8Hz), 7.40-7.55(2H, m), 7.69(2H, d, J=8Hz), 8.08(1H, d, J=8Hz), 11.44(1H, s) IR spectrum ν(KBr) cm^{-1}: 1666, 1314, 1158

Table 44



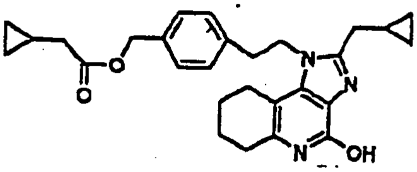
	Properties
Ref. Ex.174	light yellow crystals NMR spectrum δ (DMSO-d_6) ppm: 1.10-1.20(6H, m), 3.16(2H, t, J=7Hz), 3.45-3.60(4H, m), 4.40(2H, s), 4.78(2H, t, J=7Hz), 5.05(2H, s), 5.13(2H, s), 7.20-7.25(2H, m), 7.30-7.35(3H, m), 7.45-7.55(2H, m), 8.08(1H, d, J=8Hz), 11.48(1H, s) IR spectrum ν(KBr) cm^{-1}: 1680 Mass spectrum m/z: 463(M^+)

Table 45



	R^A	R^C	Properties
Ref. Ex.175	SO_2NH_2	Me	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 1.65-1.80(4H, m), 2.21(3H, s), 2.45-2.60(2H, m), 2.75-2.85(2H, m), 3.07(2H, t, J=7.5Hz), 4.39(2H, t, J=7.5Hz), 7.23(2H, br-s), 7.30(2H, d, J=8Hz), 7.74(2H, d, J=8Hz), 10.65(1H, br-s) IR spectrum V(KBr) cm^{-1}: 3364, 3252, 1654, 1332,1158
Ref. Ex.176	SO_2NH_2	Et	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 1.21(3H, t, J=7.5Hz), 1.65-1.80(4H, m), 2.45-2.60(2H, m), 2.55(2H, q, J=7.5Hz), 2.75-2.90(2H, m), 3.05(2H, t, J=7.5Hz), 4.39(2H, t, J=7.5Hz), 7.22(2H, br-s), 7.30(2H, d, J=8.5Hz), 7.73(2H, d, J=8.5Hz), 10.67(1H, br-s) IR spectrum V(KBr) cm^{-1}: 3224, 3088, 1650, 1332,1160
Ref. Ex.177	NHMs	CH_2OEt	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 1.13(3H, t, J=7Hz), 1.60-1.80(4H, m), 2.45-2.60(2H, m), 2.80-2.90(2H, m), 2.94(3H, s), 3.01(2H, t, J=8Hz), 3.49(2H, q, J=7Hz), 4.41(2H, s), 4.45(2H, t, J=8Hz), 7.09(2H, d, J=8.5Hz), 7.15(2H, d, J=8.5Hz), 9.55(1H, br-s), 10.74(1H, br-s) IR spectrum V(KBr) cm^{-1}: 3464, 1652, 1330, 1148

Table 46



	Properties
Ref. Ex.178	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 0.10-0.20(4H, m), 0.45-0.55(4H, m), 0.95-1.00(1H, m), 1.00-1.10(1H, m), 1.71(4H, br-s), 2.27(2H, d, J=6.5Hz), 2.43(2H, d, J=6.5Hz), 2.52(2H, br-s), 2.81(2H, br-s), 2.97(2H, t, J=7.5Hz), 4.37(2H, t, J=7.5Hz), 5.06(2H, s), 7.09(2H, d, J=8.5Hz), 7.27(2H, d, J=8.5Hz), 10.66(1H, br-s) IR spectrum V(KBr) cm^{-1}: 1736, 1660

Reference Example 179

4-[2-(4-chloro-2-ethoxymethyl-1H-imidazo[4,5-c]quinolin-1-

yl)ethyl]benzenesulfonamide

To a suspension containing 3.03 g of 4-[2-(2-ethoxymetyl-4-hydroxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide, 1.5 ml of triethylamine and 30 ml of toluene there was added dropwise 2.8 ml of phosphorus oxychloride at room temperature, and then the mixture was stirred at 120°C for 5 hours. The reaction solution was poured into ice water, the precipitated crystals were filtered off, and the obtained crystals were purified by column chromatography [silica gel, methylene chloride/methanol (20:1)] to obtain 1.89 g of light brown crystals.

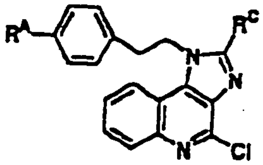
IR spectrum ν(KBr) cm^{-1} : 3360, 1332, 1160

Mass spectrum m/z : 444(M^+)

NMR spectrum δ(DMSO) ppm : 1.16(3H, t, J=7Hz), 3.30(2H, t, J=8Hz), 3.56(2H, q, J=7Hz), 4.59(2H, s), 4.99(2H, t, J=8Hz), 7.24(2H, br-s), 7.41(2H, d, J=8Hz), 7.77-7.82(4H, m), 8.11-8.13(1H, m), 8.45-8.47(1H, m)

The compounds for Reference Examples 180-196 listed in Tables 47 to 51 were obtained by the same method as Reference Example 179.

Table 47



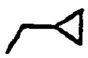
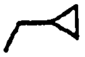
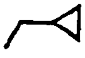
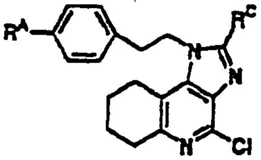
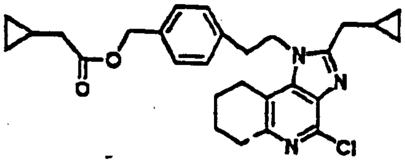
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.180	SO_2NH_2	n-Pen	light brown crystals (EtOH) mp: 212.0-213.0°C	$C_{23}H_{25}ClN_4O_2S$ Calc.: C,60.45; H,5.51; N,12.26 Found: C,60.28; H,5.46; N,12.04
Ref. Ex.181	SO_2NH_2	iso-Pen	light yellow needle-like crystals (EtOH) mp: 240.0-241.5°C	$C_{23}H_{25}ClN_4O_2S$ Calc.: C,60.45; H,5.51; N,12.26 Found: C,60.51; H,5.53; N,12.25
Ref. Ex.182	SO_2NH_2		light brown crystals ($DMF-H_2O$) mp: 266.0-270.0°C	$C_{22}H_{21}ClN_4O_2S \cdot 3/4H_2O$ Calc.: C,58.14; H,4.99; N,12.33 Found: C,58.17; H,4.79; N,12.49
Ref. Ex.183	SO_2NH_2	CF_3	light brown crystals ($DMF-H_2O$) mp: 253.0-254.0°C	$C_{19}H_{14}ClF_3N_4O_2S$ Calc.: C,50.17; H,3.10; N,12.32 Found: C,49.93; H,3.14; N,12.35
Ref. Ex.184	SO_2NH_2	$CH_2CH_2CF_3$	yellowish brown crystals ($DMF-H_2O$) mp: 239.5-241.5°C decomposition	$C_{21}H_{18}ClF_3N_4O_2S$ Calc.: C,52.23; H,3.76; N,11.60 Found: C,52.34; H,3.94; N,11.85
Ref. Ex.185	SO_2NH_2	CH_2OMe	light brown crystals ($DMF-H_2O$) mp: 234.5-235.5°C decomposition	$C_{20}H_{19}ClN_4O_3S$ Calc.: C,55.75; H,4.44; N,13.00 Found: C,56.00; H,4.17; N,13.08
Ref. Ex.186	NHMs		light brown crystals (AcOEt) mp: 205.0-206.0°C	$C_{23}H_{23}ClN_4O_2S$ Calc.: C,60.72; H,5.10; N,12.31 Found: C,60.87; H,5.14; N,12.01
Ref. Ex.187	NHMs	CH_2OEt	faint brown crystals (EtOH) mp: 198.5-200.5°C	$C_{22}H_{23}ClN_4O_3S$ Calc.: C,57.57; H,5.05; N,12.21 Found: C,57.59; H,5.04; N,12.15
Ref. Ex.188	SO_2NHMe		light brown crystals (DMF) mp: 255.5-257.0°C	$C_{23}H_{23}ClN_4O_2S$ Calc.: C,60.72; H,5.10; N,12.31 Found: C,60.62; H,5.02; N,12.26
Ref. Ex.189	SO_2NHMe	CH_2OEt	light yellow crystals ($DMF-H_2O$) mp: 214.0-215.5°C	$C_{22}H_{23}ClN_4O_3S$ Calc.: C,57.57; H,5.05; N,12.21 Found: C,57.48; H,4.90; N,12.41

Table 48



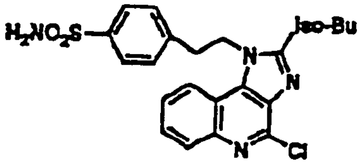
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.190	SO_2NH_2	Me	light brown crystals ($DMF-H_2O$) mp: 283.0-286.0°C	$C_{19}H_{21}ClN_4O_2S \cdot 1/4H_2O$ Calc.: C,55.74; H,5.29; N,13.68 Found: C,55.65; H,5.15; N,13.68
Ref. Ex.191	SO_2NH_2	Et	light brown crystals ($DMF-H_2O$) mp: 271.0-273.0°C	$C_{20}H_{23}ClN_4O_2S \cdot 1/4H_2O$ Calc.: C,56.73; H,5.59; N,13.23 Found: C,56.51; H,5.45; N,13.37
Ref. Ex.192	SO_2NH_2	CH_2OEt	light yellow needle-like crystals (EtOH) mp: 208.0-209.5°C	$C_{21}H_{25}ClN_4O_3S$ Calc.: C,55.18; H,5.61; N,12.48 Found: C,55.86; H,5.65; N,12.22
Ref. Ex.193	NHMs	CH_2OEt	colorless needle-like crystals (EtOH) mp: 169.5-170.0°C	$C_{22}H_{27}ClN_4O_3S$ Calc.: C,57.07; H,5.88; N,12.10 Found: C,56.77; H,5.80; N,12.02

Table 49



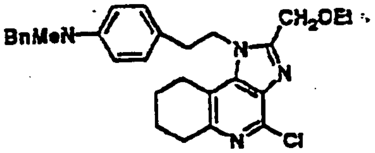
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.194	colorless crystals (Benzene-n-Hexane) mp: 109.0-110.5°C	$C_{28}H_{32}ClN_3O_2$ Calc.: C,70.35; H,6.75; N,8.79 Found: C,70.18; H,6.74; N,8.88

Table 50



	Properties
Ref. Ex.195	brown crystals NMR spectrum δ (DMSO-d_6) ppm: 0.93(6H, d, J=7Hz), 2.10-2.20(1H, m), 2.47(2H, d, J=7Hz), 3.25(2H, t, J=7Hz), 4.91(2H, t, J=7Hz), 7.23(2H, br-s), 7.29(2H, d, J=8.5Hz), 7.73(2H, d, J=8.5Hz), 7.75-7.80(2H, m), 8.05-8.15(1H, m), 8.40-8.50(1H, m) IR spectrum ν(KBr) cm^{-1}: 1332, 1160

Table 51



	Properties
Ref. Ex.196	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.20(3H, t, J=7Hz), 1.80-2.00(4H, m), 2.97(2H, t, J=7.5Hz), 3.00-3.10(2H, m), 3.01(3H, s), 3.10-3.20(2H, m), 3.52(2H, q, J=7Hz), 4.43(2H, s), 4.52(2H, s), 4.57(2H, t, J=7.5Hz), 6.65(2H, d, J=8.5Hz), 6.85(2H, d, J=8.5Hz), 7.20(2H, d, J=7.5Hz), 7.24(1H, t, J=7.5Hz), 7.31(2H, t, J=7.5Hz) IR spectrum ν(liq) cm^{-1}: 3424 Mass spectrum m/z: 488, 490(3:1, M^+)

Reference Example 197

N-[4-[(2-(4-dibenzylamino)-2-ethoxymethyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]phenyl]acetamide

A mixture of 5.21 g of N-[4-[2-[(3-amino-2-dibenzylaminoquinolin-4-yl)amino]ethyl]phenyl]acetamide and 4.21 g of ethoxyacetic acid was stirred at 140°C for 10 hours. Ethyl acetate and a 10% sodium hydroxide aqueous solution were added to the reaction mixture for separation, and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layers were combined, and after washing with saturated saline and dewatering, the solvent was distilled off. The residue was purified by column chromatography [silica gel, ethyl acetate/n-hexane (1:2-1:1)] and washed with a mixed solution of ethyl acetate and isopropyl ether to obtain 2.35 g of light brown crystals. Recrystallization from ethyl acetate yielded colorless needle-like crystals with a melting point of 171.0-171.5°C.

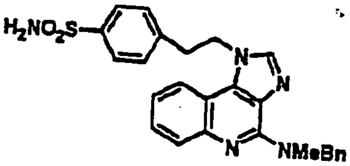
Elemental analysis: $C_{37}H_{37}N_5O_2$

Calculated: C, 76.13; H, 6.39; N, 12.00

Found: C, 76.23; H, 6.32; N, 11.98

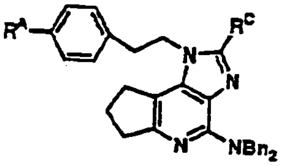
The compounds for Reference Examples 198-204 listed in Tables 52 to 56 were obtained by the same method as Reference Example 197.

Table 52



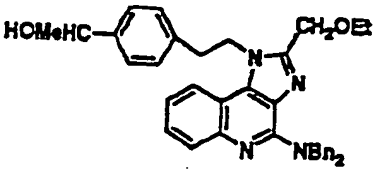
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.198	light yellow crystals (AcOEt) mp: 188.5-189.0°C	$C_{26}H_{25}N_5O_2S$ Calc.: C,66.22; H,5.34; N,14.85 Found: C,66.01; H,5.35; N,14.72

Table 53



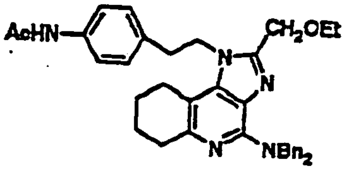
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.199	NBn_2	H	light brown crystals (AcOEt) mp: 161.5-162.0°C	$C_{45}H_{43}N_5$ Calc.: C,82.66; H,6.63; N,10.71 Found: C,82.59; H,6.76; N,10.71
Ref. Ex.200	SO_2NH_2	H	colorless crystals (MeOH) mp: 160.0-161.0°C	$C_{31}H_{31}N_5O_2S \cdot 1/2H_2O$ Calc.: C,68.11; H,5.90; N,12.81 Found: C,68.20; H,5.93; N,12.77

Table 54



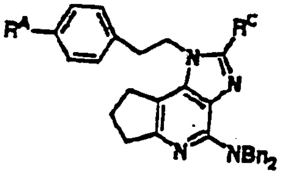
	Properties
Ref. Ex.201	orange liquid NMR spectrum δ ($CDCl_3$) ppm: 1.17(3H, t, J=7Hz), 1.49(3H, d, J=6.5Hz), 1.78(1H, br-s), 3.27(2H, t, J=7.5Hz), 3.45(2H, q, J=7Hz), 4.39(2H, s), 4.81(2H, t, J=7.5Hz), 4.90(1H, q, J=6.5Hz), 5.43(4H, br-s), 7.14(2H, d, J=8Hz), 7.15-7.40(13H, m), 7.51(1H, t, J=8Hz), 7.86(1H, d, J=8Hz), 8.13(1H, d, J=8Hz) IR spectrum V(liq) cm^{-1}: 3420

Table 55



	Properties
Ref. Ex.202	light brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.15(3H, t, J=7Hz), 1.89(4H, br-s), 2.17(3H, s), 2.84(2H, br-s), 3.05(2H, t, J=7.5Hz), 3.11(2H, br-s), 3.43(2H, q, J=6.5Hz), 4.36(2H, s), 4.52(2H, t, J=7.5Hz), 5.24(4H, s), 7.05(2H, d, J=8Hz), 7.15-7.35(10H, m), 7.41(2H, d, J=8Hz) IR spectrum V(liq) cm^{-1}: 3304, 1668, 1096 Mass spectrum m/z: 587(M^+)

Table 56



	R^A	R^C	Properties
Ref. Ex.203	NBn_2	Et	yellow liquid NMR spectrum δ ($CDCl_3$) ppm: 1.22(3H, t, J=7.5Hz), 2.17(2H, quintet, J=7.5Hz), 2.47(2H, q, J=7.5Hz),2.87(2H, t, J=7.5Hz), 2.91(2H, t, J=7.5Hz), 3.17(2H, t, J=7.5Hz), 4.21(2H, t, J=7.5Hz), 4.63(4H, s), 5.27(4H, s), 6.63(2H, d, J=8.5Hz), 6.84(2H, d, J=8.5Hz), 7.1-7.4(20H, m) Mass spectrum m/z: 681(M^+)
Ref. Ex.204	NBn_2	CH_2OEt	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.14(3H, t, J=7Hz), 2.18(2H, quintet, J=7.5Hz), 2.92(2H, t, J=7.5Hz), 2.95(2H, t, J=7.5Hz), 3.21(2H, t, J=7.5Hz), 3.42(2H, q, J=7Hz), 4.35(2H, s), 4.35(2H, t, J=7.5Hz), 4.63(4H, s), 5.25(4H, s), 6.65(2H, d, J=8.5Hz), 6.90(2H, d, J=8.5Hz), 7.18(2H, t, J=7.5Hz), 7.20-7.30(14H, m), 7.32(4H, t, J=7.5Hz)

Reference Example 205

4-[2-(2-acetoxymethyl-4-hydroxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide

To 7.53 g of 4-[2-(4-hydroxy-2-hydroxymethyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide there were added 225 ml of pyridine and 17.8 ml of acetic anhydride, and the mixture was stirred at room temperature for one hour. After concentrating the reaction solution under reduced pressure, water was added, and the precipitated crystals were filtered off and washed first with water and then with ethyl acetate to obtain 7.81 g of crystals. Recrystallization from a mixed solution of N,N-dimethylformamide and water yielded light brown crystals with a melting point of 275.0-276.0°C.

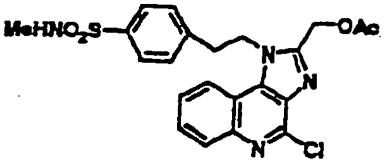
Elemental analysis: $C_{21}H_{20}N_4O_5S$

Calculated: C, 57.26; H, 4.58; N, 12.72

Found: C, 56.94; H, 4.50; N, 12.63

The compound for Reference Example 206 listed in Table 57 was obtained by the same method as Reference Example 205.

Table 57



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.206	light brown crystals (DMF-H_2O) mp: 242.0-244.0°C	$C_{22}H_{22}N_4O_5S$ Calc.: C,58.14; H,4.88; N,12.33 Found: C,58.07; H,4.59; N,12.17

Reference Example 207

4-[2-(2-hydroxymethyl-4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide

A mixture of 3.00 g of 4-[2-(2-acetoxymethyl-4-hydroxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide and 45 ml of phosphorus oxychloride was refluxed for one hour. After cooling, the crystals were filtered off and washed with ethyl acetate to obtain 2.30 g of light brown crystals. After adding 4.71 g of phenol and 1.72 g of potassium hydroxide to the obtained light brown crystals, the mixture was stirred at 120°C for one hour. After cooling, 10% hydrochloric acid and ethyl acetate were added, filtering off of the insoluble portion was followed by separation, and the ethyl acetate layer was dewatered and concentrated under reduced pressure. Diethyl ether was added to the residue, and the precipitated crystals were filtered off to obtain 1.39 g of crystals. Recrystallization from a mixed solution of N,N-dimethylformamide and water yielded light brown crystals with a melting point of 261.0-263.0°C.

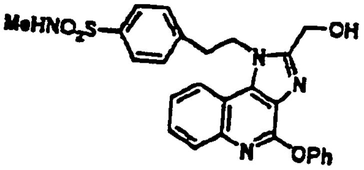
Elemental analysis: $C_{25}H_{22}N_4O_4S$

Calculated: C, 63.28; H, 4.67; N, 11.81

Found: C, 63.24; H, 4.58; N, 11.71

The compound for Reference Example 208 listed in Table 58 was obtained by the same method as Reference Example 207.

Table 58



	Properties
Ref. Ex.208	light brown crystals NMR spectrum δ (DMSO-d_6) ppm: 2.38(3H, d, J=5Hz), 3.34(2H, t, J=7.5Hz), 4.56(2H, d, J=5.5Hz), 5.02(2H, t, J=7.5Hz), 5.69(1H, t, J=5.5Hz), 7.25-7.31(4H, m), 7.43(2H, d, J=8Hz), 7.45-7.50(2H, m), 7.55-7.65(2H, m), 7.71(2H, d, J=8Hz), 7.70-7.75(1H, m), 8.35-8.37(1H, m) IR spectrum ν(KBr) cm^{-1}: 3464, 1666, 1316, 1162

Reference Example 209

4-[2-(4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzamide

To 1.65 g of 4-[2-(4-chloro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzamide there were added 0.81 g of potassium hydroxide and 4.43 g of phenol, and the mixture was stirred at 120°C for 4.5 hours. After adding water and 10% hydrochloric acid to the reaction mixture to adjust the liquid to pH 8, ethyl acetate was added and the precipitated crystals were filtered off to obtain 1.29 g of light brown crystals. Recrystallization from ethanol yielded yellow needle-like crystals with a melting point of 265.0-266.0°C.

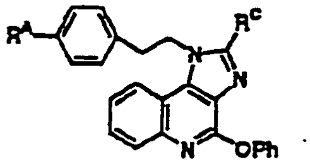
Elemental analysis: $C_{25}H_{20}N_4O_2$

Calculated: C, 73.51; H, 4.94; N, 13.72

Found: C, 73.33; H, 4.85; N, 13.43

The compounds for Reference Examples 210-287 listed in Tables 59 to 71 were obtained by the same method as Reference Example 209.

Table 59



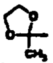
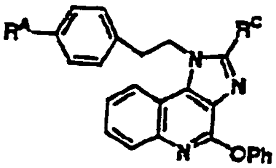
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.210	CONHMe	H	faint violet crystals (EtOH) mp: 215.0-217.0°C	$C_{26}H_{22}N_4O_2$ Calc.: C,73.92; H,5.25; N,13.26 Found: C,74.02; H,5.13; N,13.16
Ref. Ex.211	OH	H	faint brown crystals (EtOH) mp: 266.0-268.0°C	$C_{24}H_{19}N_3O_2$ Calc.: C,75.57; H,5.02; N,11.02 Found: C,75.37; H,4.72; N,11.09
Ref. Ex.212		H	colorless crystals (EtOH) mp: 193.0-195.0°C	$C_{28}H_{25}N_3O_3$ Calc.: C,74.48; H,5.58; N,9.31 Found: C,74.42; H,5.45; N,9.38
Ref. Ex.213	SO_2NHEt	H	light brown crystals ($DMF-H_2O$) mp: 257.0-259.0°C	$C_{26}H_{24}N_4O_3S$ Calc.: C,66.08; H,5.12; N,11.86 Found: C,66.11; H,4.97; N,12.12
Ref. Ex.214	SO_2NHnPr	H	colorless crystals ($DMF-H_2O$) mp: 231.5-235.0°C	$C_{27}H_{26}N_4O_3S$ Calc.: C,66.65; H,5.39; N,11.51 Found: C,66.54; H,5.32; N,11.80
Ref. Ex.215	SO_2NMe_2	H	light reddish brown crystals ($DMF-H_2O$) mp: 204.5-205.5°C	$C_{26}H_{24}N_4O_3S$ Calc.: C,66.08; H,5.12; N,11.86 Found: C,65.80; H,4.91; N,11.64
Ref. Ex.216	SO_2NH_2	H	light brown crystals ($DMF-H_2O$) mp: 260.0-260.5°C	$C_{24}H_{20}N_4O_3S$ Calc.: C,64.85; H,4.54; N,12.60 Found: C,64.58; H,4.27; N,12.56
Ref. Ex.217	SO_2NH_2	Et	light brown crystals (CH_3CN) mp: 277.0-280.0°C	$C_{26}H_{24}N_4O_3S$ Calc.: C,66.08; H,5.12; N,11.86 Found: C,65.83; H,4.83; N,11.75
Ref. Ex.218	SO_2NH_2	n-Pr	light brown crystals ($DMF-H_2O$) mp: 225.0-226.0°C	$C_{27}H_{26}N_4O_3S$ Calc.: C,66.65; H,5.39; N,11.51 Found: C,66.57; H,5.27; N,11.56
Ref. Ex.219	SO_2NH_2	n-Bu	light yellow needle-like crystals (CH_2Cl_2-MeOH) mp: 233.5-234.5°C	$C_{28}H_{28}N_4O_3S$ Calc.: C,67.18; H,5.64; N,11.19 Found: C,66.84; H,5.57; N,10.93
Ref. Ex.220	SO_2NH_2	n-Pen	light brown crystals (CH_3CN) mp: 168.5-169.5°C	$C_{29}H_{30}N_4O_3S$ Calc.: C,67.68; H,5.88; N,10.89 Found: C,67.49; H,5.71; N,10.73
Ref. Ex.221	SO_2NH_2	iso-Pen	colorless needle-like crystals (CH_3CN) mp: 225.0-226.5°C	$C_{29}H_{30}N_4O_3S$ Calc.: C,67.68; H,5.88; N,10.89 Found: C,67.42; H,5.83; N,10.78

Table 60



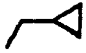
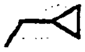
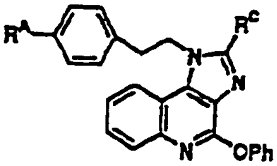
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.222	SO_2NH_2		yellow crystals	$C_{28}H_{25}N_4O_3S\cdot Na$ Calc.: C,64.60; H,4.84; N,10.76 Found: C,64.92; H,4.96; N,10.87
Ref. Ex.223	SO_2NH_2	CF_3	colorless crystals ($DMF-H_2O$) mp: 250.5-251.0°C	$C_{25}H_{19}F_3N_4O_3S$ Calc.: C,58.59; H,3.74; N,10.93 Found: C,58.38; H,3.55; N,10.83
Ref. Ex.224	SO_2NH_2	$CH_2CH_2CF_3$	light brown crystals ($DMF-H_2O$) mp: 227.5-228.5°C	$C_{27}H_{23}F_3N_4O_3S$ Calc.: C,59.99; H,4.29; N,10.36 Found: C,60.10; H,4.20; N,10.30
Ref. Ex.225	SO_2NH_2	CH_2OH	light brown crystals ($DMF-H_2O$) mp: 261.0-263.0°C	$C_{25}H_{22}N_4O_4S$ Calc.: C,63.28; H,4.67; N,11.81 Found: C,63.24; H,4.58; N,11.71
Ref. Ex.226	SO_2NH_2	CH_2OMe	colorless crystals ($DMF-H_2O$) mp: 247.0-249.0°C	$C_{26}H_{24}N_4O_4S$ Calc.: C,63.92; H,4.95; N,11.47 Found: C,63.63; H,4.80; N,11.44
Ref. Ex.227	SO_2NH_2	CH_2OEt	light yellow crystals ($DMF-H_2O$) mp: 257.0-258.0°C	$C_{27}H_{26}N_4O_4S$ Calc.: C,64.52; H,5.21; N,11.15 Found: C,64.29; H,5.13; N,10.94
Ref. Ex.228	SO_2NHMe	H	colorless crystals ($DMF-H_2O$) mp: 261.0-262.5°C	$C_{25}H_{22}N_4O_3S$ Calc.: C,65.48; H,4.84; N,12.22 Found: C,65.28; H,4.64; N,11.92
Ref. Ex.229	SO_2NHMe	Me	colorless crystals ($DMF-H_2O$) mp: 253.5-254.0°C	$C_{26}H_{24}N_4O_3S\cdot 1/4H_2O$ Calc.: C,65.46; H,5.18; N,11.74 Found: C,65.57; H,4.95; N,11.84
Ref. Ex.230	SO_2NHMe	Et	light reddish brown crystals ($DMF-H_2O$) mp: 235.5-236.0°C	$C_{27}H_{26}N_4O_3S$ Calc.: C,66.65; H,5.39; N,11.51 Found: C,66.31; H,5.24; N,11.35
Ref. Ex.231	SO_2NHMe	n-Pr	light reddish brown crystals ($DMF-H_2O$) mp: 220.0-221.5°C	$C_{28}H_{28}N_4O_3S$ Calc.: C,67.18; H,5.64; N,11.19 Found: C,67.19; H,5.55; N,11.01
Ref. Ex.232	SO_2NHMe	n-Bu	light brown crystals (EtOH) mp: 203.0-203.5°C	$C_{29}H_{30}N_4O_3S$ Calc.: C,67.68; H,5.88; N,10.89 Found: C,67.69; H,5.73; N,10.92
Ref. Ex.233	SO_2NHMe		colorless crystals (CH_3CN) mp: 225.0-226.0°C	$C_{29}H_{28}N_4O_3S$ Calc.: C,67.95; H,5.51; N,10.93 Found: C,67.95; H,5.40; N,10.89

Table 61



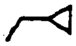
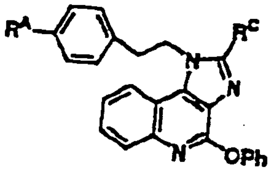
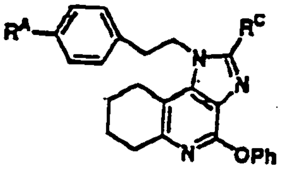
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.234	CH_2OH	H	light brown plate crystals (EtOH) mp: 187.0-189.0°C	$C_{25}H_{21}N_3O_2$ Calc.: C,75.93; H,5.35; N,10.63 Found: C,76.10; H,5.11; N,10.71
Ref. Ex.235	CH_2OH	Et	light brown crystals (DMF-H_2O) mp: 220.0-222.0°C	$C_{27}H_{25}N_3O_2$ Calc.: C,76.57; H,5.95; N,9.92 Found: C,76.28; H,6.03; N,10.01
Ref. Ex.236	CH_2OH	n-Bu	light brown crystals (EtOH) mp: 149.5-150.5°C	$C_{29}H_{29}N_3O_2$ Calc.: C,77.14; H,6.47; N,9.31 Found: C,76.99; H,6.40; N,9.14
Ref. Ex.237	NHMs	H	colorless crystals (CH_2Cl_2-MeOH) mp: 256.5-257.5°C	$C_{25}H_{22}N_4O_3S$ Calc.: C,65.48; H,4.84; N,12.22 Found: C,65.34; H,4.76; N,12.40
Ref. Ex.238	NHMs	Me	colorless crystals (CH_3CN) mp: 246.0-247.0°C	$C_{26}H_{24}N_4O_3S$ Calc.: C,66.08; H,5.12; N,11.86 Found: C,66.35; H,5.11; N,11.80
Ref. Ex.239	NHMs	Et	colorless crystals (DMF-H_2O) mp: 267.0-268.0°C	$C_{27}H_{26}N_4O_3S$ Calc.: C,66.65; H,5.39; N,11.51 Found: C,66.81; H,5.32; N,11.54
Ref. Ex.240	NHMs	n-Pr	light brown crystals (DMF-H_2O) mp: 223.0-225.5°C	$C_{28}H_{28}N_4O_3S$ Calc.: C,67.18; H,5.64; N,11.19 Found: C,67.02; H,5.55; N,11.15
Ref. Ex.241	NHMs	n-Bu	light brown crystals (DMF-H_2O) mp: 160.5-162.5°C	$C_{29}H_{30}N_4O_3S$ Calc.: C,67.68; H,5.88; N,10.89 Found: C,67.50; H,5.77; N,10.84
Ref. Ex.242	NHMs		grayish brown crystals (AcOEt) mp: 226.0-227.0°C	$C_{29}H_{28}N_4O_3S$ Calc.: C,67.95; H,5.51; N,10.93 Found: C,67.66; H,5.44; N,10.68
Ref. Ex.243	NHMs	CH_2OEt	faint brown crystals (DMF-H_2O) mp: 223.0-225.0°C	$C_{28}H_{28}N_4O_4S$ Calc.: C,65.10; H,5.46; N,10.84 Found: C,64.91; H,5.33; N,10.82
Ref. Ex.244	NHTs	H	light brown crystals (DMF-H_2O) mp: 242.0-242.5°C	$C_{31}H_{26}N_4O_3S$ Calc.: C,69.64; H,4.90; N,10.48 Found: C,69.47; H,4.68; N,10.44
Ref. Ex.245	NHAc	H	colorless prism crystals (EtOH) mp: 234.5-235.0°C	$C_{26}H_{22}N_4O_2$ Calc.: C,73.92; H,5.25; N,13.26 Found: C,73.84; H,5.15; N,13.19

Table 62



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.246	NHAc	Me	faint yellow plate crystals (MeOH) mp: 241.0-243.0°C	$C_{27}H_{24}N_4O_2\cdot1/2H_2O$ Calc.: C,72.79; H,5.66; N,12.58 Found: C,72.74; H,5.76; N,12.53
Ref. Ex.247	NHAc	Et	light brown crystals (MeOH) mp: 247.5-248.0°C	$C_{28}H_{26}N_4O_2$ Calc.: C,74.65; H,5.82; N,12.44 Found: C,74.71; H,5.84; N,12.46
Ref. Ex.248	NHAc	n-Bu	colorless plate crystals (AcOEt) mp: 176.5-177.0°C	$C_{30}H_{30}N_4O_2$ Calc.: C,75.29; H,6.32; N,11.71 Found: C,75.38; H,6.32; N,11.85
Ref. Ex.249	NMeAc	H	colorless crystals (AcOEt) mp: 144.0-145.0°C	$C_{27}H_{24}N_4O_2$ Calc.: C,74.29; H,5.54; N,12.84 Found: C,74.10; H,5.83; N,12.82
Ref. Ex.250	NMeAc	Me	colorless crystals (iso-PrOH) mp: 205.0-206.5°C	$C_{28}H_{26}N_4O_2\cdot1/2H_2O$ Calc.: C,73.18; H,5.92; N,12.19 Found: C,73.18; H,5.67; N,12.12
Ref. Ex.251	NMeAc	Et	faint brown needle-like crystals (AcOEt) mp: 99.0-102.0°C	$C_{29}H_{28}N_4O_2\cdot1/2H_2O$ Calc.: C,73.55; H,6.17; N,11.83 Found: C,73.72; H,6.19; N,11.85
Ref. Ex.252	NMeAc	n-Bu	colorless needle-like crystals (AcOEt) mp: 164.5-165.0°C	$C_{31}H_{32}N_4O_2$ Calc.: C,75.58; H,6.55; N,11.37 Found: C,75.62; H,6.60; N,11.31
Ref. Ex.253	NBn_2	n-Bu	colorless crystals (AcOEt) mp: 157.0-157.5°C	$C_{42}H_{40}N_4O$ Calc.: C,81.79; H,6.54; N,9.08 Found: C,81.93; H,6.56; N,9.09
Ref. Ex.254	CHMeNHAc	Et	light brown crystals (DMF-H_2O) mp: 182.0-184.0°C	$C_{30}H_{30}N_4O_2\cdot1/4H_2O$ Calc.: C,74.59; H,6.36; N,11.60 Found: C,74.80; H,6.23; N,11.63

Table 63



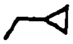
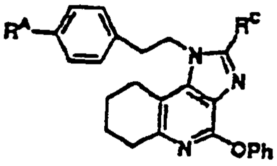
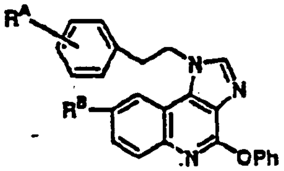
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.255	SO_2NH_2	H	light reddish brown crystals (DMF-H_2O) mp: 235.5-236.5°C	$C_{24}H_{24}N_4O_3S$ Calc.: C,64.27; H,5.39; N,12.49 Found: C,64.06; H,5.19; N,12.54
Ref. Ex.256	SO_2NH_2	Et	colorless crystals (EtOH) mp: 249.0-250.0°C	$C_{26}H_{28}N_4O_3S$ Calc.: C,65.52; H,5.92; N,11.76 Found: C,65.57; H,6.03; N,11.63
Ref. Ex.257	SO_2NH_2	CH_2OEt	light brown plate crystals (CH_3CN) mp: 250.0-252.0°C	$C_{27}H_{30}N_4O_4S$ Calc.: C,64.01; H,5.97; N,11.06 Found: C,63.99; H,6.06; N,10.70
Ref. Ex.258	CH_2OH	H	light brown crystals (iso-PrOH) mp: 188.5-190.5°C	$C_{25}H_{25}N_3O_2$ Calc.: C,75.16; H,6.31; N,10.52 Found: C,74.89; H,6.19; N,10.34
Ref. Ex.259	CH_2OH	Me	light brown crystals (iso-PrOH) mp: 201.0-202.0°C	$C_{26}H_{27}N_3O_2$ Calc.: C,74.70; H,6.63; N,10.05 Found: C,74.73; H,6.58; N, 9.86
Ref. Ex.260	CH_2OH	Et	light brown crystals (MeOH) mp: 203.5-205.0°C	$C_{27}H_{29}N_3O_2$ Calc.: C,75.85; H,6.84; N,9.83 Found: C,75.62; H,6.94; N,9.77
Ref. Ex.261	CH_2OH		light brown crystals (CH_2Cl_2-Et_2O) mp: 173.5-174.5°C	$C_{29}H_{31}N_3O_2$ Calc.: C,76.79; H,6.89; N,9.26 Found: C,76.51; H,6.61; N,8.96
Ref. Ex.262	NHMs	H	light brown crystals (DMF-H_2O) mp: 242.0-243.5°C	$C_{25}H_{26}N_4O_3S \cdot 1/2H_2O$ Calc.: C,63.67; H,5.77; N,11.88 Found: C,63.86; H,5.68; N,11.90
Ref. Ex.263	NHMs	Et	colorless crystals (MeOH) mp: 242.0-244.0°C	$C_{27}H_{30}N_4O_3S$ Calc.: C,66.10; H,6.16; N,11.42 Found: C,66.26; H,6.20; N,11.33
Ref. Ex.264	NHMs	n-Bu	colorless crystals (AcOEt) mp: 187.0-188.0°C	$C_{29}H_{34}N_4O_3S$ Calc.: C,67.15; H,6.61; N,10.80 Found: C,67.01; H,6.40; N,10.82
Ref. Ex.265	NHMs	CH_2OEt	light brown crystals (EtOH) mp: 189.0-189.5°C	$C_{28}H_{32}N_4O_4S$ Calc.: C,64.59; H,6.20; N,10.76 Found: C,64.53; H,6.20; N,10.63
Ref. Ex.266	NHAc	H	light yellow crystals (DMF-H_2O) mp: 245.0-246.5°C	$C_{26}H_{26}N_4O_2$ Calc.: C,73.22; H,6.14; N,13.13 Found: C,72.99; H,6.15; N,13.06
Ref. Ex.267	NHAc	Me	colorless needle-like crystals (EtOH) mp: 260.5-261.0°C	$C_{27}H_{28}N_4O_2$ Calc.: C,73.61; H,6.41; N,12.72 Found: C,73.45; H,6.37; N,12.73

Table 64



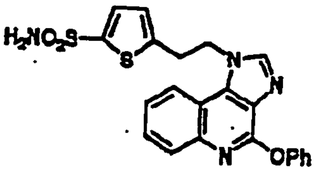
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.268	NHAc	n-Bu	light brown crystals (AcOEt) mp: 227.0-228.0°C	$C_{30}H_{34}N_4O_2$ Calc.: C,74.66; H,7.10; N,11.61 Found: C,74.57; H,7.12; N,11.48
Ref. Ex.269	NMeAc	H	colorless crystals (MeOH-H_2O) mp: 145.5-147.0°C	$C_{27}H_{28}N_4O_2$ Calc.: C,73.61; H,6.41; N,12.72 Found: C,73.58; H,6.52; N,12.66
Ref. Ex.270	NMeAc	Me	colorless prism crystals (AcOEt) mp: 181.5-182.0°C	$C_{28}H_{30}N_4O_2$ Calc.: C,73.98; H,6.65; N,12.33 Found: C,73.97; H,6.59; N,12.43
Ref. Ex.271	NMeAc	Et	faint brown crystals (AcOEt) mp: 161.0-162.5°C	$C_{29}H_{32}N_4O_2$ Calc.: C,74.33; H,6.88; N,11.96 Found: C,74.35; H,6.96; N,11.85
Ref. Ex.272	CHMeNHAc	H	colorless crystals (EtOH) mp: 236.0-236.5°C	$C_{28}H_{30}N_4O_2$ Calc.: C,73.98; H,6.65; N,12.33 Found: C,73.98; H,6.88; N,12.32

Table 65



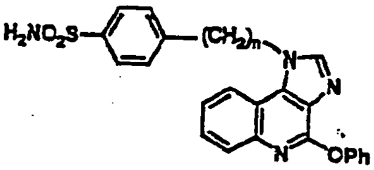
	R^A	R^B	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.273	o-SO_2NH_2	H	colorless crystals (DMF-H_2O) mp: 248.0-249.0°C	$C_{24}H_{20}N_4O_3S$ Calc.: C,64.85; H,4.54; N,12.60 Found: C,64.57; H,4.40; N,12.46
Ref. Ex.274	m-SO_2NH_2	H	light brown crystals (DMF-H_2O) mp: 255.5-257.0°C	$C_{24}H_{20}N_4O_3S \cdot 1/4H_2O$ Calc.: C,64.20; H,4.60; N,12.48 Found: C,64.01; H,4.36; N,12.64
Ref. Ex.275	p-SO_2NH_2	Cl	light brown crystals (DMF-H_2O) mp: 295.0-296.0°C	$C_{24}H_{19}ClN_4O_3S$ Calc.: C,60.19; H,4.00; N,11.70 Found: C,59.89; H,3.81; N,11.70

Table 66



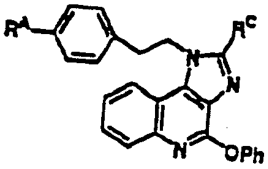
	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.276	colorless crystals (CH_2Cl_2-MeOH) mp: 240.5-241.5°C	$C_{22}H_{18}N_4O_3S_2$ Calc.: C,58.65; H,4.03; N,12.44 Found: C,58.44; H,3.75; N,12.43

Table 67



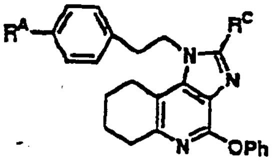
	n	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.277	1	light brown crystals (DMF-H_2O) mp: 249.0-253.5°C	$C_{23}H_{18}N_4O_3S$ Calc.: C,64.17; H,4.21; N,13.01 Found: C,63.91; H,4.13; N,12.74
Ref. Ex.278	3	light pink crystals (DMF-H_2O) mp: 255.0-255.5°C	$C_{25}H_{22}N_4O_3S$ Calc.: C,65.48; H,4.84; N,12.22 Found: C,65.44; H,4.84; N,12.11

Table 68



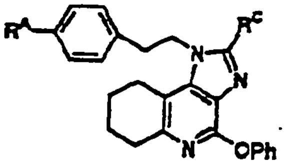
	R^A	R^C	Properties
Ref. Ex.279	SO_2NH_2	Me	light brown crystals NMR spectrum δ (DMSO-d_6), ppm: 2.28(3H, s), 3.29(2H, t, J=7Hz), 4.88(2H, t, J=7Hz), 7.24(2H, br-s), 7.20-7.35(3H, m), 7.32(2H, d, J=8Hz), 7.40-7.50(2H, m), 7.55-7.65(2H, m), 7.70-7.80(1H, m), 7.75(2H, d, J=8Hz), 8.30-8.40(1H, m) IR spectrum ν(KBr) cm^{-1}: 3324, 3152, 1312, 1156
Ref. Ex.280	SO_2NHMe	CH_2OEt	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 1.16(3H, t, J=7Hz), 2.39(3H, d, J=5Hz), 3.30(2H, t, J=7.5Hz), 3.56(2H, q, J=7Hz), 4.56(2H, s), 5.00(2H, t, J=7.5Hz), 7.28(1H, q, J=7Hz), 7.30-7.35(2H, m), 7.40-7.50(4H, m), 7.55-7.65(2H, m), 7.70-7.75(3H, m), 8.35-8.40(1H, m) IR spectrum ν(KBr) cm^{-1}: 1320, 1158 Mass spectrum m/z: 516(M^+)

Table 69



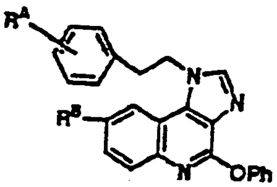
	R^A	R^C	Properties
Ref. Ex.281	SO_2NH_2	Me	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 1.70-1.90(4H, m), 2.31(3H, s), 2.68(2H, t, J=5.5Hz), 3.10(2H, t, J=5.5Hz), 3.12(2H, t, J=7.5Hz), 4.53(2H, t, J=7.5Hz), 7.08(2H, d, J=8Hz), 7.12(1H, t, J=8Hz), 7.33(2H, d, J=8Hz), 7.36(2H, t, J=8Hz), 7.75(2H, d, J=8Hz) IR spectrum ν(liq) cm^{-1}: 3328, 1316, 1160 Mass spectrum m/z: 462(M^+)

Table 70



	R^A	R^C	Properties
Ref. Ex.282	NHMs	Me	light brown crystals NMR spectrum δ ($CDCl_3$) ppm: 1.80-2.00(4H, m), 2.16(3H, s), 2.82(2H, t, J=6Hz), 2.92(3H, s), 3.04(2H, t, J=7Hz), 3.10(2H, t, J=7Hz), 4.46(2H, t, J=7Hz), 6.88(2H, d, J=8.5Hz), 7.05-7.18(5H, m), 7.28-7.32(2H, m), 7.61(1H, br-s) IR spectrum V(liq) cm^{-1}: 3432, 1338, 1158 Mass spectrum m/z: 476(M^+)
Ref. Ex.283	NHAc	Et	light brown crystals NMR spectrum δ ($DMSO-d_6$) ppm: 1.24(3H, t, J=7.5Hz), 1.75-1.85(4H, m), 2.02(3H, s), 2.63(2H, q, J=7.5Hz), 2.66(2H, t, J=6Hz), 2.96(2H, t, J=7.5Hz), 3.10(2H, t, J=6Hz), 4.46(2H, t, J=7.5Hz), 7.02(2H, d, J=8.5Hz), 7.10(2H, d, J=8.5Hz), 7.12(1H, t, J=8.5Hz), 7.37(2H, t, J=8.5Hz), 7.47(2H, d, J=8.5Hz), 9.78(1H, m) IR spectrum V(KBr) cm^{-1}: 1690, 1600, 1264
Ref. Ex.284	NMeAc	n-Bu	yellowish orange liquid NMR spectrum δ ($CDCl_3$) ppm: 0.92(3H, t, J=7.5Hz), 1.38(2H, sextet, J=7.5Hz), 1.78(2H, quintet, J=7.5Hz), 1.80-1.90(4H, m), 1.85(3H, br-s), 2.51(2H, t, J=7.5Hz), 2.80(2H, t, J=6Hz), 3.07(2H, t, J=7Hz), 3.10(2H, t, J=6Hz), 3.24(3H, s), 4.50(2H, t, J=7Hz), 7.05(2H, d, J=8Hz), 7.12(2H, d, J=8Hz), 7.13(1H, t, J=8Hz), 7.25(2H, d, J=8Hz), 7.34(2H, t, J=8Hz) IR spectrum V(liq) cm^{-1}: 3464, 1662 Mass spectrum m/z: 496(M^+)
Ref. Ex.285	NMeBn	CH_2OEt	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.19(3H, t, J=7Hz), 1.80-1.95(4H, m), 2.75-2.90(2H, m), 2.90-3.10(2H, m), 3.01(3H, s), 3.10-3.20(2H, m), 3.52(2H, q, J=7Hz), 4.44(2H, s), 4.52(2H, s), 4.57(2H, t, J=7.5Hz), 6.67(2H, d, J=8.5Hz), 6.90(2H, d, J=8.5Hz), 7.05-7.40(10H, m) IR spectrum V(liq) cm^{-1}: 3432 Mass spectrum m/z: 546(M^+)

Table 71



	R^A	R^B	Properties (recrystallization solvent)
Ref. Ex.286	p-SO_2NH_2	Me	colorless crystals NMR spectrum δ (DMSO-d_6) ppm: 2.56(3H, s), 3.33(2H, t, J=7.5Hz), 5.01(2H, t, J=7.5Hz), 7.22(2H, br-s), 7.20-7.30(3H, m), 7.37(2H, d, J=8Hz), 7.40-7.50(3H, m), 7.63(1H, d, J=8.5Hz), 7.75(2H, d, J=8Hz), 8.08(1H, s), 8.11(1H, s) IR spectrum V(KBr) cm^{-1}: 1304, 1164 Mass spectrum m/z: 458(M^+)
Ref. Ex.287	p-SO_2NH_2	OMe	grayish brown crystals NMR spectrum δ (DMSO-d_6) ppm: 3.36(2H, t, J=7Hz), 3.95(3H, s), 5.04(2H, t, J=7Hz), 7.20-7.30(4H, m), 7.22(2H, br-s), 7.38(2H, d, J=8Hz), 7.45(1H, t, J=8Hz), 7.45(1H, d, J=8Hz), 7.66(1H, d, J=2.5Hz), 7.68(1H, d, J=8Hz), 7.75(1H, d, J=8Hz), 7.75(2H, d, J=8Hz), 8.10(1H, s) IR spectrum V(KBr) cm^{-1}: 3356, 1328, 1164 Mass spectrum m/z: 474(M^+)

Reference Example 288

4-[2-(2-n-butyl-4-phenoxy-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide

(1) 4-[2-(2-n-butyl-4-chloro-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl-N-(1-ethoxypentylidene)benzenesulfonamide

To 3.04 g of 4-[2-[(3-amino-2-chloro-5,6,7,8-tetrahydroquinolin-4-yl)amino]ethyl]benzenesulfonamide there was added 12 ml of triethyl orthovalerate, and the mixture was stirred at 120-140°C for 25 hours. After adding n-hexane and removing the triethyl orthovalerate by decantation, the residue was stirred at 140°C for 19 hours. The mixture was purified by column chromatography [silica gel, methylene chloride/methanol (100:1)] to obtain 1.67 g of light brown crystals.

(2) 4-[2-(2-n-butyl-4-phenoxy-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzenesulfonamide

To 1.35 g of 4-[2-(2-n-butyl-4-chloro-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl-N-(1-ethoxypentylidene)benzenesulfonamide there were added 0.43 g of potassium hydroxide and 2.33 g of phenol, and the mixture was stirred at 120°C for 5 hours. After adding water and a 10% sodium hydroxide aqueous solution to the reaction mixture to adjust the liquid to pH 10, methylene chloride was added for extraction. After washing the extract first with a 10% sodium hydroxide aqueous solution, water and then with saturated saline and dewatering, the methylene chloride was distilled off. The residue was purified by column chromatography [silica gel, methylene chloride/methanol (100:1-30:1)] to obtain 0.68 g of faint brown crystals. Recrystallization from ethyl acetate yielded colorless crystals with a melting point of 224.5-225.5°C.

Elemental analysis: $C_{28}H_{32}N_4O_3S$

Calculated: C, 66.64; H, 6.39; N, 11.10

Found: C, 66.43; H, 6.41; N, 10.84

Reference Example 289

4-[2-(2-cyclopropylmethyl-4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol

(1) 4-[2-(4-chloro-2-cyclopropylmethyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl cyclopropylacetate

To 1.33 g of 4-[2-(2-cyclopropylmethyl-4-hydroxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl cyclopropylacetate there was added 20 ml of phosphorus oxychloride, and the mixture was stirred at 120°C for one hour. The reaction solution was poured into water, and methylene chloride was added for extraction. After washing the extract first with water and then with saturated saline and dewatering, the solvent was distilled off. The residue was purified by column chromatography [silica gel, methylene chloride/methanol (100:1-30:1)] to obtain 0.36 g of colorless crystals.

(2) 4-[2-(2-cyclopropylmethyl-4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol

To 0.25 g of 4-[2-(4-chloro-2-cyclopropylmethyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl cyclopropylacetate there were added 0.09 g of potassium hydroxide and 0.50 g of phenol, and the mixture was stirred at 120°C for 4 hours. After the reaction, water, a 10% sodium hydroxide aqueous solution and ethyl acetate were added, and the mixture was stirred while cooling on ice. The precipitated crystals were filtered off to obtain 0.14 g of faint brown crystals. Recrystallization from ethyl acetate yielded 0.10 g of colorless crystals with a melting point of 185.0-185.5°C.

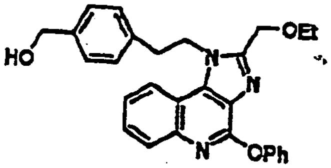
Elemental analysis: $C_{29}H_{27}N_3O_2$

Calculated: C, 77.48; H, 6.05; N, 9.35

Found: C, 77.22; H, 6.09; N, 9.11

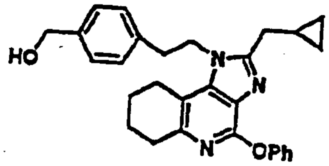
The compounds for Reference Examples 290-291 listed in Tables 72 and 73 were obtained by the same method as Reference Example 289.

Table 72



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.290	colorless crystals (AcOEt) mp: 184.5-185.0°C	$C_{28}H_{27}N_3O_3$ Calc.: C,74.15; H,6.00; N,9.27 Found: C,74.13; H,6.22; N,9.25

Table 73



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.291	light brown crystals (CH_2Cl_2-Et_2O) mp: 173.5-174.5°C	$C_{29}H_{31}N_3O_2$ Calc.: C,76.79; H,6.89; N,9.26 Found: C,76.51; H,6.61; N,8.96

Reference Example 292

4-[2-[2-(2-methylpropyl)-4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl]ethyl]benzenesulfonamide

(1) 4-[2-[4-hydroxy-2-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl]benzenesulfonamide

To 8.0 g of 4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl]benzenesulfonamide there was added 11.6 ml of isovaleric acid, and the mixture was stirred at 130°C for 24 hours. The precipitated crystals were filtered off and washed with methylene chloride to obtain 9.31 g of crystals.

(2) 4-[2-[4-chloro-2-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl]benzenesulfonamide

To 9.00 g of 4-[2-[4-hydroxy-2-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl]benzenesulfonamide there was added 135 ml of phosphorus oxychloride, and the mixture was stirred at 120°C for 9 hours. The reaction solution was concentrated under reduced pressure, ethyl acetate was added, and the precipitated crystals were filtered off to obtain 5.10 g of crystals.

(3) 4-[2-[2-(2-methylpropyl)-4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl]ethyl]benzenesulfonamide

To 4.80 g of 4-[2-[4-chloro-2-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl]benzenesulfonamide there were added 1.86 g of potassium hydroxide and 10.2 g of phenol, and the mixture was stirred at 120°C for 5 hours. After adding water and 10% hydrochloric acid to the reaction mixture to adjust the liquid to pH 8, ethyl acetate was added and the precipitated crystals were filtered off to obtain 2.16 g of light brown crystals. Recrystallization from ethyl acetate yielded light brown needle-like crystals with a melting point of 221.0-222.0°C.

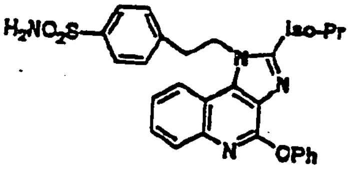
Elemental analysis: $C_{28}H_{28}N_4O_3S$

Calculated: C, 67.18; H, 5.64; N, 11.19

Found: C, 67.08; H, 5.47; N, 11.40

The compound for Reference Example 293 listed in Table 74 was obtained by the same method as Reference Example 292.

Table 74



	Properties (recrystallization solvent)	Elemental analysis
Ref. Ex.293	light yellow needle-like crystals (CH_3CN) mp: 261.0-263.0°C	$C_{27}H_{26}N_4O_3S$ Calc.: C,66.65; H,5.39; N,11.51 Found: C,66.51; H,5.24; N,11.53

Reference Example 294

1-[2-(4-cyanophenyl)ethyl]-4-phenoxy-1H-imidazo[4,5-c]quinoline

After dissolving 1.33 g of 4-[2-(4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzamide in 33 ml of N,N-dimethylformamide, 1.05 ml of pyridine and 0.92 ml of trifluoroacetic anhydride were added while stirring on ice, and stirring on ice was continued for 30 minutes. After adding 100 ml of ice water and 20 ml of diethyl ether to the reaction solution and stirring, the precipitated crystals were filtered off to obtain 0.89 g of crystals. Recrystallization from ethyl acetate yielded light yellow needle-like crystals with a melting point of 196.0-198.0°C.

Elemental analysis: $C_{25}H_{18}N_4O$

Calculated: C, 76.91; H, 4.65; N, 14.35

Found: C, 76.97; H, 4.35; N, 14.45

Reference Example 295

4-[2-(4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl] benzoic acid

To 2.31 g of ethyl 4-[2-(4-chloro-1H-imidazo[4,5-c]quinolin-1-yl)ethyl] benzoate there were added 5.67 g of phenol and 2.02 g of potassium hydroxide, and the mixture was stirred at 120°C for 3 hours. After adding water and 10% hydrochloric acid to the reaction mixture to adjust the liquid to pH 8, ethyl acetate was added and the precipitated crystals were filtered off to obtain 2.29 g of crystals. Recrystallization from a mixed solution of N,N-dimethylformamide and water yielded colorless crystals with a melting point of 265.0-267.0°C.

Elemental analysis: $C_{25}H_{19}N_3O_3$
Calculated: C, 73.34; H, 4.68; N, 10.26
Found: C, 73.34; H, 4.38; N, 10.38

Example 1

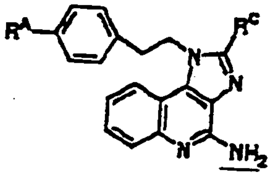
4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzamide

To 1.09 g of 4-[2-(4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzamide there was added 9.87 g of ammonium acetate, and the mixture was stirred at 140°C for 5 hours. After adding a 10% sodium hydroxide aqueous solution to the reaction mixture to adjust the liquid to pH 8, the precipitated crystals were filtered off and washed with water to obtain 0.82 g of light brown crystals. Recrystallization from ethanol yielded light brown crystals with a melting point of 267.0-268.0°C.

Elemental analysis: $C_{19}H_{17}N_5O$
Calculated: C, 68.87; H, 5.17; N, 21.13
Found: C, 68.58; H, 4.94; N, 20.87

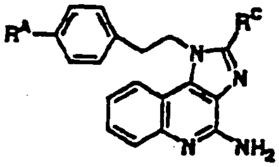
The compounds for Examples 2-50 listed in Tables 75 to 78 were obtained by the same method as Example 1.

Table 75



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 2	CONHMe	H	faint brown crystals (MeOH) mp: 264.5-266.0°C	$C_{20}H_{19}N_5O$ Calc.: C,69.55; H,5.54; N,20.28 Found: C,69.69; H,5.43; N,20.04
Ex. 3	OH	H	faint yellow needle-like crystals (EtOH) mp: 257.0-259.0°C	$C_{18}H_{16}N_4O$ Calc.: C,71.04; H,5.30; N,18.41 Found: C,70.76; H,5.04; N,18.32
Ex. 4	CN	H	yellow crystals (DMF) mp: 301.0-303.0°C	$C_{19}H_{15}N_5$ Calc.: C,72.83; H,4.82; N,22.35 Found: C,72.87; H,4.57; N,22.32
Ex. 5	COOH	H	faint brown crystals (reprecipitated) mp: ≥300°C	$C_{19}H_{16}N_4O_2 \cdot 1/3H_2O$ Calc.: C,67.45; H,4.96; N,16.56 Found: C,67.38; H,4.71; N,16.51
Ex. 6	SO_2NHEt	H	light yellow crystals (DMF-H_2O) mp: 207.5-209.5°C	$C_{20}H_{21}N_5O_2S$ Calc.: C,60.74; H,5.35; N,17.71 Found: C,60.88; H,5.26; N,17.57
Ex. 7	SO_2NH-n-Pr	H	colorless crystals (DMF-H_2O) mp: 199.0-200.0°C	$C_{21}H_{23}N_5O_2S$ Calc.: C,61.59; H,5.66; N,17.10 Found: C,61.47; H,5.56; N,17.33
Ex. 8	SO_2NMe_2	H	faint yellow needle-like crystals (DMF) mp: 297.5-298.5°C	$C_{20}H_{21}N_5O_2S$ Calc.: C,60.74; H,5.35; N,17.71 Found: C,60.44; H,5.49; N,17.55
Ex. 9	SO_2NH_2	H	light brown crystals (DMF) mp: 298.5-299.0°C	$C_{18}H_{17}N_5O_2S$ Calc.: C,58.84; H,4.66; N,19.06 Found: C,58.59; H,4.66; N,18.95
Ex. 10	SO_2NH_2	Me	light brown crystals (DMF-H_2O) mp: 274.0-275.0°C	$C_{19}H_{19}N_5O_2S \cdot 1/4H_2O$ Calc.: C,59.13; H,5.09; N,18.15 Found: C,59.17; H,5.41; N,18.10
Ex. 11	SO_2NH_2	Et	light yellowish brown crystals (DMF-EtOH) mp: 283.0-284.0°C	$C_{20}H_{21}N_5O_2S$ Calc.: C,60.74; H,5.35; N,17.71 Found: C,60.43; H,5.21; N,17.41
Ex. 12	SO_2NH_2	n-Pr	light brown needle-like crystals (EtOH) mp: 242.5-244.0°C	$C_{21}H_{23}N_5O_2S$ Calc.: C,61.59; H,5.66; N,17.10 Found: C,61.47; H,5.56; N,16.81
Ex. 13	SO_2NH_2	n-Bu	light yellow needle-like crystals (EtOH) mp: 257.0-258.0°C	$C_{22}H_{25}N_5O_2S \cdot 1/4H_2O$ Calc.: C,61.73; H,6.00; N,16.36 Found: C,61.93; H,6.08; N,16.12
Ex. 14	SO_2NH_2	n-Pen	light brown crystals (EtOH) mp: 244.0-244.5°C	$C_{23}H_{27}N_5O_2S$ Calc.: C,63.13; H,6.22; N,16.01 Found: C,63.31; H,6.29; N,16.04

Table 76



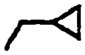
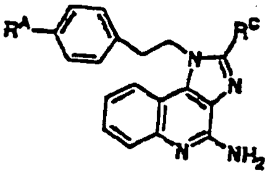
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 15	SO_2NH_2	iso-Pr	colorless needle-like crystals (CH_3CN-EtOH) mp: 265.5-266.0°C	$C_{21}H_{23}N_5O_2S \cdot 1/5H_2O$ Calc.: C,61.06; H,5.71; N,16.95 Found: C,60.76; H,5.62; N,16.78
Ex. 16	SO_2NH_2	iso-Bu	light brown crystals (CH_2Cl_2-MeOH) mp: 232.0-234.0°C	$C_{22}H_{25}N_5O_2S$ Calc.: C,62.39; H,5.95; N,16.54 Found: C,62.57; H,5.95; N,16.35
Ex. 17	SO_2NH_2	iso-Pen	colorless crystals (DMF-H_2O) mp: 249.5-253.5°C	$C_{23}H_{27}N_5O_2S$ Calc.: C,63.13; H,6.22; N,16.01 Found: C,62.92; H,6.38; N,15.87
Ex. 18	SO_2NH_2		light yellow needle-like crystals (MeOH) mp: 245.5-248.5°C	$C_{22}H_{23}N_5O_2S$ Calc.: C,62.69; H,5.50; N,16.61 Found, C,62.52; H,5.33; N,16.50
Ex. 19	SO_2NH_2	CF_3	colorless crystals (DMF-H_2O) mp: 286.5-287.0°C	$C_{19}H_{16}F_3N_5O_2S$ Calc.: C,52.41; H,3.70; N,16.08 Found: C,52.38; H,3.66; N,15.87
Ex. 20	SO_2NH_2	$CH_2CH_2CF_3$	light brown crystals (DMF-H_2O) mp: 248.5-249.0°C	$C_{21}H_{20}F_3N_5O_2S$ Calc.: C,54.42; H,4.35; N,15.11 Found: C,54.13; H,4.49; N,14.91
Ex. 21	SO_2NH_2	CH_2OH	faint yellow crystals (EtOH-H_2O) mp: 256.0-258.0°C	$C_{19}H_{19}N_5O_3S \cdot 1/3H_2O$ Calc.: C,56.56; H,4.91; N,17.36 Found: C,56.87; H,4.66; N,17.55
Ex. 22	SO_2NH_2	CH_2OMe	colorless crystals (DMF) mp: 248.0-249.0°C	$C_{20}H_{21}N_5O_3S$ Calc.: C,58.38; H,5.14; N,17.02 Found: C,58.50; H,5.03; N,16.76
Ex. 23	SO_2NH_2	CH_2OEt	colorless crystals (DMF-H_2O) mp: 272.5-274.5°C	$C_{21}H_{23}N_5O_3S$ Calc.: C,59.28; H,5.45; N,16.46 Found: C,59.07; H,5.36; N,16.16
Ex. 24	SO_2NHMe	H	colorless crystals (DMF-H_2O) mp: 244.0-245.0°C	$C_{19}H_{19}N_5O_2S$ Calc.: C,59.83; H,5.02; N,18.36 Found: C,59.83; H,4.94; N,18.27
Ex. 25	SO_2NHMe	Me	colorless crystals (DMF-H_2O) mp: 259.5-260.5°C	$C_{20}H_{21}N_5O_2S$ Calc.: C,60.74; H,5.35; N,17.71 Found: C,60.88; H,5.33; N,17.43
Ex. 26	SO_2NHMe	Et	colorless crystals (DMF) mp: 262.0-264.0°C	$C_{21}H_{23}N_5O_2S$ Calc.: C,61.59; H,5.66; N,17.10 Found: C,61.69; H,5.65; N,16.86

Table 77



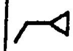
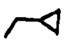
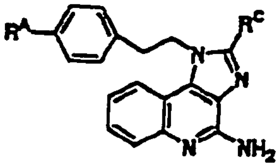
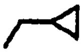
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 27	SO_2NHMe	n-Pr	colorless crystals (DMF) mp: 233.5-234.5°C	$C_{22}H_{25}N_5O_2S$ Calc.: C,62.39; H,5.95; N,16.54 Found: C,62.36; H,5.91; N,16.24
Ex. 28	SO_2NHMe	n-Bu	light brown crystals (MeOH) mp: 225.5-226.5°C	$C_{23}H_{27}N_5O_2S$ Calc.: C,63.13; H,6.22; N,16.01 Found: C,63.04; H,6.25; N,15.81
Ex. 29	SO_2NHMe	CH_2OH	faint yellow plate crystals (MeOH) mp: ≥300°C	$C_{20}H_{21}N_5O_3S \cdot HCl \cdot 1/4H_2O$ Calc.: C,53.09; H,5.01; N,15.48 Found: C,53.09; H,5.20; N,15.18
Ex. 30	SO_2NHMe		faint brown crystals (DMF) mp: 231.0-232.0°C	$C_{23}H_{25}N_5O_2S$ Calc.: C,63.43; H,5.79; N,16.08 Found: C,63.44; H,5.79; N,15.95
Ex. 31	SO_2NHMe	CH_2OEt	colorless crystals (DMF-H_2O) mp: 239.0-240.5°C	$C_{22}H_{25}N_5O_3S$ Calc.: C,60.12; H,5.73; N,15.93 Found: C,59.98; H,5.75; N,15.78
Ex. 32	CH_2OH	H	light brown crystals (EtOH) mp: 223.0-225.5°C	$C_{19}H_{18}N_4O$ Calc.: C,71.68; H,5.70; N,17.60 Found: C,71.84; H,5.48; N,17.36
Ex. 33	CH_2OH	Et	colorless crystals (MeOH) mp: 215.5-217.0°C	$C_{21}H_{22}N_4O$ Calc.: C,72.81; H,6.40; N,16.17 Found: C,72.94; H,6.44; N,16.17
Ex. 34	CH_2OH	n-Bu	light brown crystals (MeOH) mp: 289.0-289.5°C	$C_{23}H_{26}N_4O \cdot HCl$ Calc.: C,67.22; H,6.62; N,13.63 Found: C,66.99; H,6.89; N,13.62
Ex. 35	CH_2OH		light brown prism crystals (MeOH) mp: ≥289.0°C, decomposed	$C_{23}H_{24}N_4O \cdot HCl \cdot 1/2H_2O$ Calc.: C,66.10; H,6.27; N,13.41 Found: C,66.25; H,6.06; N,13.55
Ex. 36	CH_2OH	CH_2OEt	colorless crystals (EtOH) mp: 241.0-242.0°C	$C_{22}H_{24}N_4O_2 \cdot HCl$ Calc.: C,63.99; H,6.10; N,13.57 Found: C,64.13; H,6.10; N,13.37
Ex. 37	NHMs	H	colorless crystals (AcOEt) mp: 229.5-230.5°C	$C_{19}H_{19}N_5O_2S$ Calc.: C,59.83; H,5.02; N,18.36 Found: C,59.57; H,4.94; N,18.20
Ex. 38	NHMs	Me	colorless crystals (CH_3CN-EtOH) mp: 228.0-229.0°C	$C_{20}H_{21}N_5O_2S$ Calc.: C,60.74; H,5.35; N,17.71 Found: C,60.77; H,5.34; N,17.47

Table 78



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 39	NHMs	Et	colorless prism crystals (MeOH) mp: 180.5-181.5°C	$C_{21}H_{23}N_5O_2S \cdot HCl \cdot 3/2H_2O$ Calc.: C,53.32; H,5.75; N,14.81 Found: C,53.39; H,5.72; N,14.82
Ex. 40	NHMs	n-Pr	light brown crystals (iso-PrOH) mp: 250.5-253.5°C	$C_{22}H_{25}N_5O_2S \cdot HCl$ Calc.: C,57.44; H,5.70; N,15.22 Found: C,57.18; H,5.63; N,14.99
Ex. 41	NHMs	n-Bu	light brown crystals (MeOH) mp: 250.5-253.5°C	$C_{23}H_{27}N_5O_2S \cdot HCl$ Calc.: C,58.28; H,5.95; N,14.77 Found: C,58.25; H,5.85; N,14.79
Ex. 42	NHMs		colorless crystals (MeOH) mp: 235.0-235.5°C	$C_{23}H_{25}N_5O_2S \cdot HCl$ Calc.: C,58.53; H,5.55; N,14.84 Found: C,58.44; H,5.41; N,14.82
Ex. 43	NHMs	CH_2OEt	faint brown crystals (EtOH) mp: 218.0-220.0°C	$C_{22}H_{25}N_5O_3S$ Calc.: C,60.12; H,5.73; N,15.93 Found: C,59.85; H,5.63; N,15.69
Ex. 44	NHTs	H	light brown crystals (DMF-H_2O) mp: 236.5-237.5°C	$C_{25}H_{23}N_5O_2S$ Calc.: C,65.63; H,5.07; N,15.31 Found: C,65.44; H,4.92; N,15.11
Ex. 45	NHAc	H	colorless crystals (CH_2Cl_2-MeOH) mp: 247.0-248.0°C	$C_{20}H_{19}N_5O \cdot 1/4H_2O$ Calc.: C,68.65; H,5.61; N,20.01 Found: C,68.59; H,5.43; N,20.00
Ex. 46	NHAc	Me	colorless crystals (EtOH-H_2O) mp: ≥290°C, decomposed	$C_{21}H_{21}N_5O \cdot HCl$ Calc.: C,63.71; H,5.60; N,17.69 Found: C,63.61; H,5.64; N,17.78
Ex. 47	NHAc	Et	colorless crystals (MeOH-H_2O) mp: 293.5-294.5°C, decomposed	$C_{22}H_{23}N_5O \cdot HCl$ Calc.: C,64.46; H,5.90; N,17.08 Found: C,64.52; H,6.03; N,17.06
Ex. 48	NHAc	n-Bu	colorless crystals (CH_2Cl_2-MeOH) mp: ≥300°C	$C_{24}H_{27}N_5O \cdot HCl$ Calc.: C,65.82; H,6.58; N,15.89 Found: C,65.63; H,6.44; N,15.99
Ex. 49	NBn_2	n-Bu	colorless crystals (AcOEt) mp: 177.0-178.0°C	$C_{36}H_{37}N_5$ Calc.: C,80.11; H,6.91; N,12.98 Found: C,79.93; H,6.85; N,12.75
Ex. 50	CHMeNHAc	Et	colorless crystals (MeOH) mp: 154.0-155.5°C	$C_{24}H_{27}N_5O \cdot 1/2H_2O$ Calc.: C,70.22; H,6.87; N,17.06 Found: C,70.46; H,6.78; N,17.05

Example 51

4-[2-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol

(1) 4-[2-(4-chloro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol

To 2.57 g of 4-[2-[(3-amino-2-chloroquinolin-4-yl)amino]ethyl]benzyl alcohol there was added 7.2 ml of triethyl orthoacetate, and the mixture was stirred at 120-140°C for 28 hours. After adding n-hexane to the reaction mixture and removing it by decantation, the residue was purified by column chromatography [silica gel, methylene chloride/methanol (1:0-30:1)] to obtain 1.66 g of light yellow crystals.

(2) 4-[2-(2-methyl-4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol

To 1.50 g of 4-[2-(4-chloro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol there were added 0.73 g of potassium hydroxide and 4.02 g of phenol, and the mixture was stirred at 120°C for 6 hours. After adding water and a 10% sodium hydroxide aqueous solution to the reaction mixture to adjust the liquid to pH 10, methylene chloride was added for extraction. The methylene chloride layer was washed first with a 10% sodium hydroxide aqueous solution, water and then with saturated saline, and after dewatering, the solvent was distilled off under reduced pressure to obtain 1.20 g of light brown crystals.

(3) 4-[2-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol

To 1.00 g of 4-[2-(2-methyl-4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzyl alcohol there was added 4.52 g of ammonium acetate, and the mixture was stirred at 140°C for 6 hours. After the reaction, a 10% sodium hydroxide aqueous solution was added to adjust the liquid to pH 8, and then extraction was performed with a mixed solution of methylene chloride and methanol (10:1). The organic layer was concentrated under reduced pressure, 3.8 ml of methanol and 0.2 ml of a 2 N sodium hydroxide aqueous solution were added to the residue, and the mixture was stirred at 50°C for one hour. The reaction solution was stirred on ice to obtain 0.26 g of crystals. Recrystallization from ethanol yielded colorless crystals with a melting point of 236.0-237.0°C.

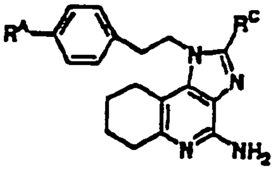
Elemental analysis: $C_{20}H_{20}N_4O$

Calculated: C, 72.27; H, 6.06; N, 16.86

Found: C, 72.05; H, 6.07; N, 16.64

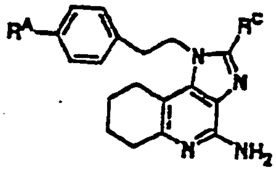
The compounds for Examples 52-79 listed in Tables 79 to 84 were obtained by the same method as Example 1.

Table 79



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 52	SO_2NH_2	H	light brown crystals (DMF-H_2O) mp: 292.5-294.0°C	$C_{18}H_{21}N_5O_2S \cdot 1/8H_2O$ Calc.: C,57.85; H,5.73; N,18.74 Found: C,57.73; H,5.48; N,18.49
Ex. 53	SO_2NH_2	Me	colorless crystals (MeOH) mp: 261.5-263.0°C	$C_{19}H_{23}N_5O_2S \cdot 3/4H_2O$ Calc.: C,57.19; H,6.19; N,17.55 Found: C,57.39; H,5.95; N,17.27
Ex. 54	SO_2NH_2	Et	colorless crystals (MeOH) mp: 281.0-283.0°C	$C_{20}H_{25}N_5O_2S \cdot 1/2H_2O$ Calc.: C,58.80; H,6.41; N,17.14 Found: C,58.59; H,6.15; N,17.17
Ex. 55	SO_2NH_2	n-Bu	light brown crystals (EtOH) mp: 240.0-241.0°C	$C_{22}H_{29}N_5O_2S$ Calc.: C,61.80; H,6.84; N,16.38 Found: C,61.52; H,6.85; N,16.17
Ex. 56	SO_2NH_2	CH_2OEt	light brown plate crystals (EtOH) mp: 254.5-256.0°C	$C_{21}H_{27}N_5O_3S$ Calc.: C,58.72; H,6.34; N,16.30 Found: C,59.02; H,6.43; N,16.16
Ex. 57	CH_2OH	H	colorless crystals (EtOH) mp: 223.5-225.0°C	$C_{19}H_{22}N_4O$ Calc.: C,70.78; H,6.88; N,17.38 Found: C,70.90; H,6.84; N,17.30
Ex. 58	CH_2OH	Me	light brown crystals (iso-PrOH) mp: 230.0-231.0°C	$C_{20}H_{24}N_4O$ Calc.: C,71.40; H,7.19; N,16.65 Found: C,71.31; H,7.37; N,16.40
Ex. 59	CH_2OH	Et	colorless crystals (EtOH) mp: 222.5-224.5	$C_{21}H_{26}N_4O$ Calc.: C,71.97; H,7.48; N,15.99 Found: C,71.70; H,7.48; N,16.05

Table 80



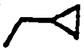
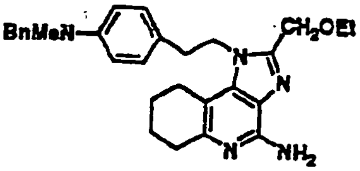
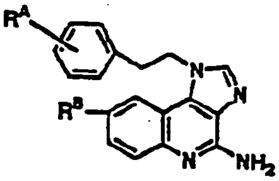
	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 60	CH_2OH		light brown crystals (THF) mp: 231.5-232.5°C	$C_{23}H_{28}N_4O$ Calc.: C,73.37; H,7.50; N,14.88 Found: C,73.34; H,7.60; N,14.70
Ex. 61	NHMs	H	light brown crystals (MeOH) mp: 271.5-274.0°C	$C_{19}H_{23}N_5O_2S\cdot HCl\cdot 1/4H_2O$ Calc.: C,53.51; H,5.79; N,16.42 Found: C,53.64; H,5.88; N,16.30
Ex. 62	NHMs	Me	light brown crystals (MeOH) mp: 292.0-293.0°C	$C_{20}H_{25}N_5O_2S\cdot 2HCl$ Calc.: C,50.85; H,5.76; N,14.82 Found: C,51.00; H,5.95; N,14.77
Ex. 63	NHMs	Et	light brown crystals (iso-PrOH) mp: 202.5-204.0°C	$C_{21}H_{27}N_5O_2S$ Calc.: C,60.99; H,6.58; N,16.94 Found: C,60.96; H,6.46; N,16.80
Ex. 64	NHMs	n-Bu	colorless crystals (EtOH) mp: 275.0-276.5°C	$C_{23}H_{31}N_5O_2S\cdot 2HCl$ Calc.: C,53.69; H,6.46; N,13.61 Found: C,53.86; H,6.36; N,13.49
Ex. 65	NHMs	CH_2OEt	light brown needle-like crystals (EtOH) mp: 296.0-297.0°C	$C_{22}H_{29}N_5O_3S\cdot HCl$ Calc.: C,55.05; H,6.30; N,14.59 Found: C,55.01; H,6.27; N,14.42
Ex. 66	NHAc	H	light brown crystals (DMF) mp: 294.0-295.5°C	$C_{20}H_{23}N_5O\cdot HCl\cdot 1/4H_2O$ Calc.: C,61.53; H,6.33; N,17.94 Found: C,61.46; H,6.33; N,18.04
Ex. 67	NHAc	Me	light brown crystals (THF) mp: 236.0-237.0°C	$C_{21}H_{25}N_5O\cdot 1/4H_2O$ Calc.: C,68.54; H,6.99; N,19.03 Found: C,68.76; H,7.00; N,18.76
Ex. 68	NHAc	Et	light brown crystals ($MeOH-H_2O$) mp: 134.0-135.5°C	$C_{22}H_{27}N_5O\cdot H_2O$ Calc.: C,66.81; H,7.39; N,17.71 Found: C,66.67; H,7.59; N,17.43
Ex. 69	NHAc	n-Bu	light brown crystals (MeOH) mp: ≥300°C	$C_{24}H_{31}N_5O\cdot HCl\cdot 1/2H_2O$ Calc.: C,63.91; H,7.38; N,15.53 Found: C,64.07; H,7.17; N,15.70
Ex. 70	CHMeNHAc	H	colorless crystals (EtOH) mp: 253.0-254.0°C, decomposed	$C_{22}H_{27}N_5O\cdot HCl$ Calc.: C,63.83; H,6.82; N,16.92 Found: C,63.53; H,6.89; N,16.86

Table 81



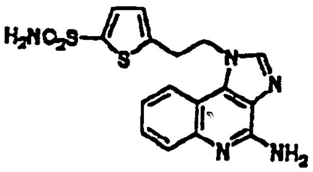
	Properties
Ex. 71	brown liquid NMR spectrum δ ($CDCl_3$) ppm: 1.20(3H, t, J=7Hz), 1.80-2.00(4H, m), 2.80-3.15(6H, m), 3.01(3H, s), 3.51(2H, q, J=7Hz), 4.36(2H, s), 4.49(2H, t, J=7.5Hz), 4.52(2H, s), 5.39(2H, br-s), 6.66(2H, d, J=8.5Hz), 6.89(2H, d, J=8.5Hz), 7.12-7.40(5H, m) IR spectrum ν(liq) cm^{-1}: 3320, 3180 Mass spectrum m/z: 469(M^+)

Table 82



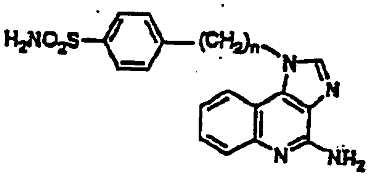
	R^A	R^B	Properties (recrystallization solvent)	Elemental analysis
Ex. 72	o-SO_2NH_2	H	light yellow crystals (DMF-H_2O) mp: 273.0-274.0°C	$C_{18}H_{17}N_5O_2S$ Calc.: C,58.84; H,4.66; N,19.06 Found: C,58.62; H,4.51; N,18.85
Ex. 73	m-SO_2NH_2	H	light brown crystals (DMF-H_2O) mp: 258.5-260.0°C	$C_{18}H_{17}N_5O_2S$ Calc.: C,58.84; H,4.66; N,19.06 Found: C,58.56; H,4.47; N,19.12
Ex. 74	p-SO_2NH_2	Me	colorless crystals (EtOH) mp: 257.0-257.5°C	$C_{19}H_{19}N_5O_2S$ Calc.: C,59.83; H,5.02; N,18.36 Found: C,59.53; H,4.79; N,18.16
Ex. 75	p-SO_2NH_2	OMe	light brown needle-like crystals (DMF-H_2O) mp: 277.0-278.0°C	$C_{19}H_{19}N_5O_3S$ Calc.: C,57.42; H,4.82; N,17.62 Found: C,57.08; H,4.66; N,17.47
Ex. 76	p-SO_2NH_2	Cl	light brown crystals (EtOH) mp: 277.0-278.0°C	$C_{18}H_{16}ClN_5O_2S \cdot 9/8H_2O$ Calc.: C,51.21; H,4.35; N,16.50 Found: C,51.42; H,4.19; N,16.22

Table 83



	Properties (recrystallization solvent)	Elemental analysis
Ex. 77	colorless crystals (EtOH) mp: 238.0-239.0°C	$C_{16}H_{15}N_{5}O_{2}S_{2}$ Calc.: C,51.46; H,4.05; N,18.75 Found: C,51.25; H,3.91; N,18.47

Table 84



	n	Properties (recrystallization solvent)	Elemental analysis
Ex. 78	1	light brown crystals (DMF-H_2O) mp: 297.0-299.5°C	$C_{17}H_{15}N_{5}O_{2}S\cdot1/8H_2O$ Calc.: C,57.41; H,4.32; N,19.69 Found: C,57.19; H,4.07; N,19.40
Ex. 79	3	light brown crystals (DMF-H_2O) mp: 289.5-290.5°C	$C_{19}H_{19}N_{5}O_{2}S\cdot1/6H_2O$ Calc.: C,59.36; H,5.07; N,18.22 Found: C,59.47; H,4.85; N,18.02

Example 80

N-[4-[2-(4-amino-2-ethoxymethyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]phenyl]acetamide

A suspension of 2.20 g of N-[4-[2-(4-dibenzylamino-2-ethoxymethyl-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]phenyl]acetamide, 4.00 g of Perlman's reagent and 14.28 g of ammonium formate in 70 ml of methanol was refluxed for 53 hours. The catalyst was filtered off, and the solvent was distilled off under reduced pressure. Water and saturated saline were added to the residue and extraction was performed with methylene chloride. After dewatering the extract, the solvent was distilled off under reduced pressure. The obtained residue was washed with isopropyl ether to obtain 1.24 g of colorless crystals. Recrystallization from isopropan 1 yielded colorless crystals with a melting point of 207.0-208.0°C.

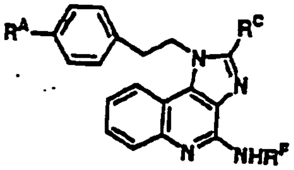
Elemental analysis: $C_{23}H_{25}N_5O_2 \cdot 1/2H_2O$

Calculated: C, 66.97; H, 6.35; N, 16.98

Found: C, 66.90; H, 6.28; N, 16.81

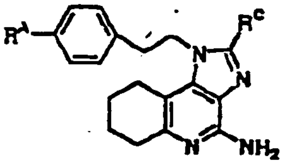
The compounds for Examples 81-84 listed in Tables 85 to 87 were obtained by the same method as Example 80.

Table 85



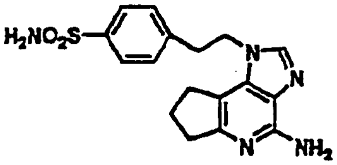
	R^A	R^C	R^F	Properties (recrystallization solvent)	Elemental analysis
Ex. 81	CHMeOH	CH_2OEt	H	colorless crystals (EtOH) mp: 231.5-232.0°C	$C_{23}H_{26}N_4O_2$ Calc.: C,70.75; H,6.71; N,14.35 Found: C,70.66; H,6.74; N,14.32
Ex. 82	SO_2NH_2	H	Me	light yellow crystals (AcOEt) mp: 188.5-189.0°C	$C_{26}H_{25}N_5O_2S$ Calc.: C,66.22; H,5.34; N,14.85 Found: C,66.01; H,5.35; N,14.72

Table 86



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 83	NHAc	CH_2OEt	colorless crystals (MeOH) mp: ≥300°C	$C_{23}H_{29}N_5O_2 \cdot HCl$ Calc.: C,62.22; H,6.81; N,15.77 Found: C,62.00; H,6.87; N,15.74

Table 87



	Properties (recrystallization solvent)	Elemental analysis
Ex. 84	colorless crystals (MeOH) mp: 275.0-275.5°C	$C_{17}H_{19}N_5O_2S \cdot 1/4H_2O$ Calc.: C,56.42; H,5.43; N,19.43 Found: C,56.72; H,5.26; N,19.18

Example 85

1-[2-(4-aminophenyl)ethyl]-1H-imidazo[4,5-c]quinoline-4-amine·hydrochloride

To 8.00 g of N-[4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]phenyl]acetamide there was added 40 ml of 2 N hydrochloric acid, and the mixture was stirred at 120°C for one hour. After the reaction, a 10% sodium hydroxide aqueous solution was added to adjust the liquid to pH 7, and then the precipitated crystals were filtered off and purified by column chromatography [silica gel, methylene chloride/methanol (20:1)], after which ethanolic hydrogen chloride was added and the precipitated crystals were filtered off to obtain 3.50 g of colorless crystals. Recrystallization from a mixed solution of methanol and water yielded colorless crystals with a melting point of 275.0-283.0°C.

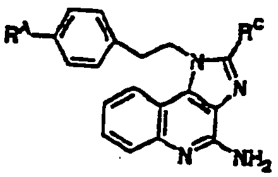
Elemental analysis: $C_{18}H_{17}N_5 \cdot 2HCl \cdot 1/4H_2O$

Calculated: C, 56.78; H, 5.16; N, 18.39

Found: C, 56.78; H, 5.11; N, 18.22

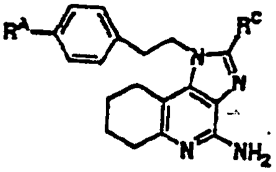
The compounds for Examples 86-104 listed in Tables 88 and 89 were obtained by the same method as Example 85.

Table 88



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 86	NH_2	Me	light brown crystals (THF) mp: 235.0-236.0°C	$C_{19}H_{19}N_5$ Calc.: C,71.90; H,6.03; N,22.07 Found: C,71.89; H,6.24; N,21.81
Ex. 87	NH_2	Et	faint brown crystals ($MeOH-H_2O$) mp: 202.0-203.0°C	$C_{20}H_{21}N_5$ Calc.: C,72.48; H,6.39; N,21.13 Found: C,72.64; H,6.33; N,20.95
Ex. 88	NH_2	n-Bu	faint brown crystals (AcOEt) mp: 187.0-188.0°C	$C_{22}H_{25}N_5$ Calc.: C,73.51; H,7.01; N,19.48 Found: C,73.78; H,6.93; N,19.34
Ex. 89	NH_2	CH_2OEt	colorless crystals (iso-PrOH) mp: 208.0-208.5°C	$C_{21}H_{23}N_5O$ Calc.: C,69.78; H,6.41; N,19.38 Found: C,69.85; H,6.40; N,19.38
Ex. 90	NHMe	H	colorless crystals (MeOH) mp: 245.0-246.0°C	$C_{19}H_{19}N_5 \cdot 2HCl \cdot 5/4H_2O$ Calc.: C,55.28; H,5.74; N,16.96 Found: C,55.39; H,5.52; N,16.98
Ex. 91	NHMe	Me	light brown crystals (EtOH) mp: 275.0-276.5°C	$C_{20}H_{21}N_5 \cdot 2HCl \cdot 3/2H_2O$ Calc.: C,55.69; H,6.08; N,16.24 Found: C,55.76; H,6.20; N,16.09
Ex. 92	NHMe	Et	light brown crystals (EtOH) mp: 271.0-273.0°C	$C_{21}H_{23}N_5 \cdot 2HCl \cdot H_2O$ Calc.: C,57.80; H,6.24; N,16.05 Found: C,57.80; H,6.15; N,15.95
Ex. 93	NHMe	n-Bu	light grayish brown crystals (EtOH) mp: 173.0-175.0°C, decomposed	$C_{23}H_{27}N_5 \cdot 3HCl \cdot 1/4H_2O$ Calc.: C,56.68; H,6.30; N,14.37 Found: C,56.97; H,6.59; N,14.08
Ex. 94	NHMe	CH_2OEt	colorless crystals (AcOEt) mp: 156.0-156.5°C	$C_{22}H_{25}N_5O$ Calc.: C,70.38; H,6.71; N,18.65 Found: C,70.29; H,6.44; N,18.49

Table 89



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 95	NH_2	H	light brown crystals (MeOH) mp: 264.0-265.0°C	$C_{18}H_{21}N_5 \cdot 2HCl$ Calc.: C,56.85; H,6.10; N,18.41 Found: C,56.93; H,6.10; N,18.42
Ex. 96	NH_2	Me	light brown crystals (AcOEt) mp: 192.0-193.0°C	$C_{19}H_{23}N_5$ Calc.: C,71.00; H,7.21; N,21.79 Found: C,70.98; H,7.34; N,21.49
Ex. 97	NH_2	Et	faint yellow crystals (EtOH) mp: ≥285°C, decomposed	$C_{20}H_{25}N_5 \cdot 2HCl \cdot 5/4H_2O$ Calc.: C,55.75; H,6.90; N,16.25 Found: C,55.80; H,6.81; N,16.29
Ex. 98	NH_2	n-Bu	light yellow crystals (iso-PrOH) mp: 245.0-252.0°C, decomposed	$C_{22}H_{29}N_5 \cdot 2HCl \cdot 3/4H_2O$ Calc.: C,58.73; H,7.28; N,15.57 Found: C,58.51; H,7.20; N,15.38
Ex. 99	NH_2	CH_2OEt	colorless crystals (EtOH) mp: 259.0-260.0°C	$C_{21}H_{27}N_5O \cdot 2HCl$ Calc.: C,57.53; H,6.67; N,15.98 Found: C,57.52; H,6.80; N,15.83
Ex. 100	NHMe	H	light brown crystals (EtOH) mp: 224.5-225.5°C	$C_{19}H_{23}N_5 \cdot 2HCl \cdot H_2O$ Calc.: C,55.34; H,6.60; N,16.98 Found: C,55.17; H,6.56; N,17.13
Ex. 101	NHMe	Me	light brown crystals (EtOH) mp: 284.0-285.0°C	$C_{20}H_{25}N_5 \cdot 2HCl \cdot 7/2H_2O$ Calc.: C,50.96; H,7.27; N,14.86 Found: C,50.89; H,7.20; N,14.79
Ex. 102	NHMe	Et	brown crystals (EtOH) mp: 274.0-285.0°C, decomposed	$C_{21}H_{27}N_5 \cdot 2HCl \cdot 3H_2O$ Calc.: C,52.94; H,7.40; N,14.70 Found: C,52.71; H,7.21; N,14.69
Ex. 103	NHMe	n-Bu	colorless crystals (EtOH), mp: 161.0-163.5°C, decomposed	$C_{23}H_{31}N_5 \cdot 3HCl \cdot 5/4H_2O$ Calc.: C,54.23; H,7.22; N,13.75 Found: C,54.28; H,7.40; N,13.83
Ex. 104	$CHMeNH_2$	H	light brown crystals (EtOH) mp: 207.0-210.0°C, decomposed	$C_{20}H_{25}N_5 \cdot 2HCl \cdot H_2O$ Calc.: C,56.34; H,6.86; N,16.43 Found: C,56.38; H,6.78; N,16.39

Example 105

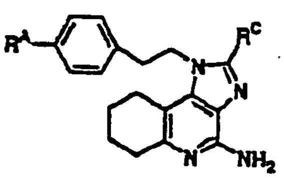
1-[2-(4-aminophenyl)ethyl]-2-n-butyl-1H-imidazo[4,5-c]quinoline-4-amine

A suspension of 18.8 g of 1-[2-[4-(dibenzylamino)phenyl]ethyl]-2-n-butyl-1H-imidazo[4,5-c]quinoline-4-amine, 3.76 g of Perlman's reagent, 33.0 g of ammonium formate and 600 ml of methanol was refluxed for 7 hours. The catalyst was filtered off and the solvent was distilled off. Water was added to the obtained residue, the liquid was adjusted to pH 9 with a 10% sodium hydroxide aqueous solution, and extraction was performed with methylene chloride. After washing the extract with water and dewatering, the solvent was distilled off and the obtained residue was washed with ethyl acetate and recrystallized from isopropanol to obtain colorless crystals with a melting point of 191.0-192.0°C.

Elemental analysis: $C_{22}H_{25}N_5$
Calculated: C, 73.51; H, 7.01; N, 19.48
Found: C, 73.41; H, 6.90; N, 19.22

The compound for Example 106 listed in Table 90 was obtained by the same method as Example 105.

Table 90



	R^A	R^C	Properties (recrystallization solvent)	Elemental analysis
Ex. 106	NHMe	CH_2OEt	light brown crystals - (AcOEt) mp: 127.0-128.5°C	$C_{22}H_{29}N_5O$ Calc.: C,69.63; H,7.70; N,18.45 Found: C,69.67; H,7.69; N,18.17

Example 107

1-[2-(4-aminophenyl)ethyl]-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine·hydrochloride

A mixture of 0.81 g of N,N-dibenzyl-1-[2-[4-(dibenzylamino)phenyl]ethyl]-1,6,7,8-tetrahydrocyclopenta[b]imidazo[4,5-d]pyridine-4-amine, 0.16 g of Perlman's reagent, 1.56 g of ammonium formate and 40 ml of methanol was refluxed for 30.5 hours. The catalyst was filtered off, and the solvent was distilled off. Water was added to the residue, the liquid was adjusted to pH 9 with a 10% potassium carbonate aqueous solution, and methylene chloride was added. The precipitated crystals were filtered off, and after separating off the methylene chloride layer, the aqueous layer was further extracted with methylene chloride. The methylene chloride layer was dewatered, and then the solvent was distilled off to obtain colorless crystals. These were combined with the previous crystals and a common method was used to obtain 0.41 g of colorless crystals as a hydrochloride. Recrystallization from methanol yielded colorless crystals with a melting point of 259.0-260.0°C (decomposed).

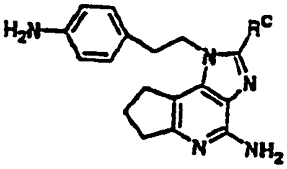
Elemental analysis: $C_{17}H_{19}N_5 \cdot 2HCl$

Calculated: C, 55.74; H, 5.78; N, 19.12

Found: C, 55.76; H, 5.89; N, 19.07

The compounds for Examples 108-109 listed in Table 91 were obtained by the same method as Example 107.

Table 91



	R`	Properties (recrystallization solvent)	Elemental analysis
Ex. 108	Et	light yellowish brown crystals (EtOH) mp: 266.0-268.0°C, decomposed	$C_{19}H_{23}N_5 \cdot 2HCl \cdot 1/3EtOH \cdot H_2O$ Calc.: C,55.23; H,6.83; N,16.37 Found: C,55.24; H,6.84; N,16.57
Ex. 109	CH_2OEt	light brown crystals (EtOH) mp: 250.5-251.5°C, decomposed	$C_{20}H_{25}N_5O \cdot 2HCl \cdot 1/4H_2O$ Calc.: C,56.01; H,6.46; N,16.33 Found: C,56.23; H,6.31; N,16.08

Example 110

1-[2-(4-ureidophenyl)ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

After dissolving 800 mg of 1-[2-(4-aminophenyl)ethyl]-1H-imidazo[4,5-c]quinoline-4-amine in a mixed solution of 8 ml of acetic acid and 4.8 ml of water, a solution of 400 mg of sodium cyanate in 4.8 ml of water was added while stirring at room temperature, and stirring at room temperature was continued for 2 hours. After adding a 10% sodium hydroxide aqueous solution to the reaction solution to adjust the liquid to pH 9 and filtering off the crystals, they were washed with water to obtain 790 mg of crystals. Recrystallization from a mixed solution of ethanol and water yielded faint brown crystals with a melting point of 300°C or higher.

Elemental analysis: $C_{19}H_{18}N_6O$
Calculated: C, 65.88; H, 5.24; N, 24.26
Found: C, 66.00; H, 5.14; N, 24.07

Example 111

1-[2-[4-(N'-methylthioureido)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

To 800 mg of 1-[2-(4-aminophenyl)ethyl]-1H-imidazo[4,5-c]quinoline-4-amine there were added 24 ml of methanol and 0.60 ml of methyl isothiocyanate, and the mixture was stirred at 40°C for 15 hours. After cooling the reaction solution, the precipitated crystals were filtered off to obtain 770 mg of crystals. Recrystallization from a mixed solution of ethanol and water yielded faint brown crystals with a melting point of 220.0-221.5°C.

Elemental analysis: $C_{20}H_{20}N_6S$
Calculated: C, 63.81; H, 5.35; N, 22.32
Found: C, 63.60; H, 5.13; N, 22.05

Example 112

1-[2-(4-acetylphenyl)ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

To 3.89 g of 2-[4-[2-(4-phenoxy-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]phenyl-2-methyl-1,3-dioxolane there was added 33.2 g of ammonium acetate, and the mixture was stirred at 140°C for 3 hours. After the reaction, a 10% sodium hydroxide aqueous solution was added to adjust the liquid to pH 8, and then the precipitated crystals were filtered off and washed with water to obtain 2.83 g of light brown crystals. Recrystallization from a mixed solution of methylene chloride and methanol yielded colorless crystals with a melting point of 267.0-269.0°C.

Elemental analysis: $C_{20}H_{18}N_4O$
Calculated: C, 72.71; H, 5.49; N, 16.96
Found: C, 72.41; H, 5.34; N, 16.70

Example 113

1-[2-[4-(1-hydroxyiminoethyl)phenyl]ethyl]-1H-imidaz [4,5-c]quinoline-4-amine

To 1.63 g of 1-[2-(4-acetylphenyl)ethyl]-1H-imidazo[4,5-c]quinoline-4-amine there were added 0.38 g of hydroxylamine hydrochloride, 1.34 g of sodium acetate·$3H_2O$ and 16 ml of ethanol, and the mixture was refluxed for 2 hours. After concentrating the reaction solution under reduced pressure, water was added and the precipitated crystals were filtered off to obtain 1.47 g of crystals. Recrystallization from a mixed solution of ethanol and water yielded faint brown crystals with a melting point of 269.0-270.5°C.

Elemental analysis: $C_{20}H_{19}N_5O$
Calculated: C, 69.55; H, 5.54; N, 20.28
Found: C, 69.34; H, 5.54; N, 20.11

Example 114

1-[2-[4-(1-aminoethyl)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine

To 500 mg of 1-[2-[4-(1-hydroxyiminoethyl)phenyl]ethyl]-1H-imidazo[4,5-c]quinoline-4-amine there were added 150 ml of 10% methanolic ammonia and 1 ml of Raney nickel, and the mixture was stirred under a hydrogen pressure of 5 atmospheres at 50°C for 80 hours. After cooling the reaction solution, the solvent was filtered off and concentrated under reduced pressure to obtain 300 mg of crystals. Recrystallization from ethanol yielded faint brown crystals with a melting point of 222.0-224.0°C.

Elemental analysis: $C_{20}H_{21}N_5$
Calculated: C, 72.48; H, 6.39; N, 21.13
Found: C, 72.46; H, 6.39; N, 20.86

Example 115

Ethyl 4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl] benzoate

To 550 mg of 4-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl] benzoic acid there were added 28 ml of ethanol and 2.8

ml of concentrated sulfuric acid, and the mixture was refluxed for 5 hours. After concentrating the reaction solution under reduced pressure, water and a 10% sodium hydroxide aqueous solution were added to adjust the liquid to pH 9, and the precipitated crystals were filtered off to obtain 550 mg of light brown crystals. Recrystallization from methanol yielded light brown needle-like crystals with a melting point of 180.0-182.0°C.

Elemental analysis: $C_{21}H_{20}N_4O_2$
Calculated: C, 69.98; H, 5.59; N, 15.55
Found: C, 69.98; H, 5.39; N, 15.62

Experimental Example 1: Interferon *α* inductivity in human cells

Table 1 shows interferon *α* inductivities in human cells for the purpose of demonstrating the excellent effect of the compounds of the invention. The following compounds were used as the control agents.

Control agent A: 1-isobutyl-1H-imidazo[4,5-c]quinoline-4-amine (common name: imiquimod)

Control agent B: 1-(2-phenylethyl)-1H-imidazo[4,5-c]quinoline-4-amine

1. Preparation of blood cells for culturing

Whole blood was collected by venipuncture into a 50 ml centrifuge tube containing 170 µl of Novo Heparin Injection 1000 (Novo Nordisk A/S). Peripheral blood monocytes (PBMCs) were prepared with a Leuco PREPTM (Becton Dickinson; Reorder No. 2751) cell separation tube, and were cultured to a cell density of 1 x 106 cells/ml in RPM-1640 medium (Nissui Pharmaceuticals, KK.; Code 05918) containing 2 mM L-glutamine (LIFE TECHNOLOGIES; Cat. No. 25030-016) and a penicillin-streptomycin solution (final concentration: 100 U/ml penicillin, 100 µg/ml streptomycin, LIFE TECHNOLOGIES; Cat. No. 15145-014) to which 10% fetal bovine serum (INTERGEN COMPANY; Cat. No. 1020-90) had been added.

2. Preparation of compounds

The compounds were suspended to 1 mg/ml in 0.1 N hydrochloric acid and then solubilized by dilution with physiological saline. The compounds were tested in a concentration range of 0.03 μg/ml to 3.0 μg/ml.

3. Incubation

A 50 μl portion of the test compound solution or solvent was added to a 96-well (flat-bottom) MicroTest III™ (Becton Dickinson; FALCON 3072) cell culturing plate, and 200 μl of the PMBC in the medium was added to each full well. The plate was covered with a plastic lid and incubated for two days at 37°C in a 5% carbon dioxide atmosphere.

4. Separation

Following the incubation, the plate was coated with PLATE SEALER S (Coster Corporation; Cat. No. 3095) and then centrifuged at 2000 rpm (740xG, rotor; RS-96SA/6) in a Universal cooling centrifuge (KUBOTA 5800, manufactured by Kubota Laboratories) at 4°C for 5 minutes. The culture supernatants were used as samples.

5. Interferon *α* assay

This was accomplished by enzyme immunoassay. Using a Cytoscreen™ human interferon *α* assay kit (BIOSOURCE; Cat. #ASY-05), a 96-well plate immobilizing mouse anti-human interferon *α* monoclonal antibodies (primary antibodies) was subjected to an antigen-antibody reaction to bind the interferon *α* in 100 μl of sample. Subsequent binding of rabbit anti-human interferon *α* polyclonal antibodies (secondary antibodies) was followed by binding of anti-rabbit antibodies labeled with peroxidase. Tetramethylbenzidine was used for coloration and the reaction was terminated. The absorbance at 450 nm was then measured with a Vmax kinetic microplate reader (Molecular Devices). All of the results were obtained with the values expressed in pg/ml based on an interferon *α* standard curve. The results are shown in Tables 92 and 93.

Table 92

	Interferon α inductivity (pg/ml) Dose concentration (µg/ml)					
Compound	0.01	0.03	0.10	0.3	1	3
Example 9	12	43	387	818	619	313
Example 10	1019	953	682	436	314	191
Example 11	850	966	726	570	346	161
Example 12	15	740	860	697	337	139
Example 13	658	645	240	208	132	86
Example 18	180	557	417	222	156	103
Example 23	1018	3052	2072	1556	1233	1133
Example 42	86	668	194	167	85	35
Example 43	130	229	449	327	219	201
Example 45	-	-	67	746	879	960
Example 48	-	73	644	735	629	436
Example 50	-	-	492	1003	759	288
Example 56	843	771	620	534	580	560
Example 59	-	358	698	964	980	947
Example 62	683	777	731	785	734	849
Example 64	663	796	711	649	651	606
Example 65	-	992	607	519	419	-
Example 67	8840	577	268	236	112	-
Example 69	664	1014	758	569	343	217
Example 70	-	-	1246	1197	931	651
Example 80	-	342	194	459	538	-
Example 83	727	778	817	589	507	-
Example 84	-	-	3	638	679	520
Example 85	0	639	745	628	600	598
Example 86	905	469	173	123	79	-
Example 87	-	732	571	763	717	-
Example 88	-	459	491	607	545	-

Table 93

	Interferon α inductivity (pg/ml) Dose concentration (μg/ml)					
Compound	0.01	0.03	0.10	0.3	1	3
Example 89	-	602	493	756	768	-
Example 94	-	869	875	794	771	717
Example 95	-	786	475	765	553	-
Example 96	1012	1099	1336	1100	794	780
Example 98	854	263	341	233	190	-
Example 99	557	347	238	230	189	155
Example 101	135	463	760	764	598	457
Example 106	353	553	668	659	602	576
Example 107	-	-	737	336	546	381
Control agent A	-	22	29	73	50	34
Control agent B	-	28	62	69	68	49

The compounds of the invention exhibited more excellent interferon α inductivity than the control agents, and are therefore highly useful for treatment of diseases caused by viruses, such as rheumatoid arthritis, warts, hepatitis B, hepatitis C, etc. and for cancer and other neoplastic diseases.

[Effect of the Invention]

The compounds of the invention have excellent interferon inductivity and are therefore highly useful for treatment of diseases caused by viruses, such as rheumatoid arthritis, warts, hepatitis B, hepatitis C, etc. and for cancer and other neoplastic diseases.